Pediatric Critical Care Medicine
XXX 2026 • Volume 27 • Number 00 • Pages XX–XX

SPECIAL ARTICLE

Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock in Children 2026

OBJECTIVES: To update evidence-based management recommendations for clinicians caring for children (including infants, school-aged children, and adolescents) with sepsis or septic shock.

DESIGN: A panel of 68 international experts, representing 13 international organizations, as well as six methodologists, was convened. A formal conflict-of-interest policy was developed at the onset of the process and applied throughout. Teleconferences and electronic-based discussion among the chairs, co-chairs, methodologists, and subgroup leads as well as within subgroups, served as an integral part of the guideline development process.

METHODS: New priority topics and recommendations from the prior guideline iteration were used to identify Population, Intervention, Control, and Outcomes (PICO) questions likely to have new or updated evidence. We conducted a systematic review to identify the best available evidence, summarized the evidence, and then assessed the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation approach. We used the evidence-to-decision framework to formulate recommendations as strong or conditional, or as a good practice statement. "In our practice," statements were included when evidence was inconclusive to issue a recommendation but the panel felt that some guidance based on practice patterns may be appropriate.

RESULTS: The panel provided 61 statements on the management of children with sepsis or septic shock. Overall, five were strong recommendations, 24 were conditional recommendations, and ten were good practice statements. For 22 PICO questions, no recommendations could be made, but, for seven of these, "in our practice" statements were provided. Compared with the 2020 guidelines, 20 recommendations were new, 13 were updated for clarity and/or new evidence, six were reviewed but not changed, and 22 were carried forward based on consensus of the panel that new evidence was not available. Only three recommendations were based on high or moderate certainty of evidence.

CONCLUSIONS: Updated management guidelines were issued by a panel of international experts for the best care of children with sepsis or septic shock, acknowledging that most aspects of care continue to have relatively low quality of evidence.

KEYWORDS: evidence-based medicine; guidelines; infection; pediatrics; sepsis; septic shock; Surviving Sepsis Campaign

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This article is simultaneously published in the journals *Pediatric Critical Care Medicine* (10.1097/PCC.0000000000003927) and *Intensive Care Medicine* (10.1007/s00134-026-08360-2). All Rights Reserved.

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DOI: 10.1097/PCC.0000000000003927

Sepsis remains a leading cause of morbidity, mortality, and healthcare utilization for children worldwide (1, 2). Early identification and appropriate management remain critically important to optimize both short- and long-term outcomes for children with sepsis and septic shock (3).

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In 2020, the first Surviving Sepsis Campaign guidelines specific to pediatrics were published as a joint effort of the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM). This current iteration provides updated guidance for clinicians caring for infants, preschool and school-aged children, and adolescents with sepsis or septic shock in a hospital, emergency, or acute care setting (although some may be applicable in other settings). However, these recommendations do not necessarily establish a definitive treatment algorithm or a single standard of care for all patients (4). Rather, recommendations were developed to be broadly applicable, acknowledging that variation of resources within and across healthcare systems and geographic regions will determine the practical application of these guidelines. These guidelines also do not replace clinicians' judgment or decision-making when presented with unique clinical scenarios.

METHODS

The Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock in Children guidelines were fully funded by SCCM and ESICM. Sponsoring professional societies supported the participation of their representatives. There was no industry support. Complete details on the scope, sponsorship, panel selection and organization, Population, Intervention, Control, and Outcomes (PICO) question selection, outcome prioritization, literature search strategy and evidence summation, certainty of evidence assessment, recommendation formulation, consensus voting, and conflict-of-interest management are presented in the **Supplementary Materials** (https://links.lww.com/PCC/C714). We highlight key aspects of the methodology here.

Panel Members: The 68-person panel included broad international and multiprofessional representation from critical and intensive care medicine, emergency medicine, anesthesiology, neonatology, infectious diseases, and psychology with inclusion of physicians, nurses, pharmacists, psychologists, and advanced practice providers. One lay member was also included with a role to ensure that patient, family, and caregivers' opinions were considered in prioritizing outcomes and discussing recommendations about long-term outcomes among sepsis survivors. Panelists were recruited from a wide number of countries and healthcare systems, including representation from resource-limited geographic areas with diversity across sex, race, and location.

Evidence Synthesis: The panel was organized into five subgroups focusing on: 1) recognition and management of infection, 2) hemodynamics and resuscitation, 3) ventilation, 4) adjunctive, metabolic, and immunologic therapies, and 5) long-term follow-up. PICO questions addressed in the prior 2020 guidelines were reviewed for continued relevance, and new PICO questions were developed with input from each subgroup. Only PICO questions that were specific to sepsis or septic shock and determined likely to have substantial new evidence published on the topic were included (further details in the Supplementary Materials, https://links.lww.com/PCC/C714). Prioritized patient-centered outcomes were selected a priori for each question. A comprehensive literature review was completed and data extraction was completed using Covidence (www.covidence.org). The methodology team, with input

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from panel members, assessed individual studies for risk of bias using the Cochrane Risk of Bias-2 tool or the CLARITY Risk of Bias tool for randomized controlled trials (RCTs) or cohort studies, respectively (5, 6). The table of studies for each PICO, including risk of bias assessment, can be found in the Supplementary Materials (https://links.lww.com/PCC/C714).

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate the certainty of evidence as high, moderate, low, or very low considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias of the total available evidence (7–11). The panel considered evidence for each PICO question in a hierarchy of indirectness. Studies focusing on children with sepsis or septic shock were prioritized, although studies inclusive of more general pediatric populations (all PICU patients) were considered on a case-by-case basis. Evidence synthesized for the concurrent adult Surviving Sepsis Campaign guideline was considered according to an a priori framework to determine appropriateness of including indirect evidence (**Fig. 1**). Evidence from adult studies was generally downgraded due to the indirectness of the evidence.

We used the evidence-to-decision (EtD) framework to support consistent, transparent, and structured formulation of statements across the guideline. The EtD framework considers the balance of effects and certainty of evidence, as well as patient values, resource intensity, equity, and cost-effectiveness. The EtD summary of judgments for each PICO question is presented in the Supplementary Materials (https://links.lww.com/PCC/C714).

For practical reasons, the panel did not address topics pertaining to general acute or critical illness, even if previously included in the 2020 guidelines (e.g., stress ulcer and venous thromboembolism prophylaxis). Instead, we refer clinicians to other guidelines on these topics, including nutrition, ventilation, transfusion, or pain and sedation management (12–16). For sepsis-specific PICO questions that remained relevant to current practice, but for which the panel a priori agreed that no new substantial evidence was available, a full literature search was not undertaken and the existing recommendations were carried forward into this new iteration (minor wording changes were allowed to ensure consistency with other new or updated terminology).

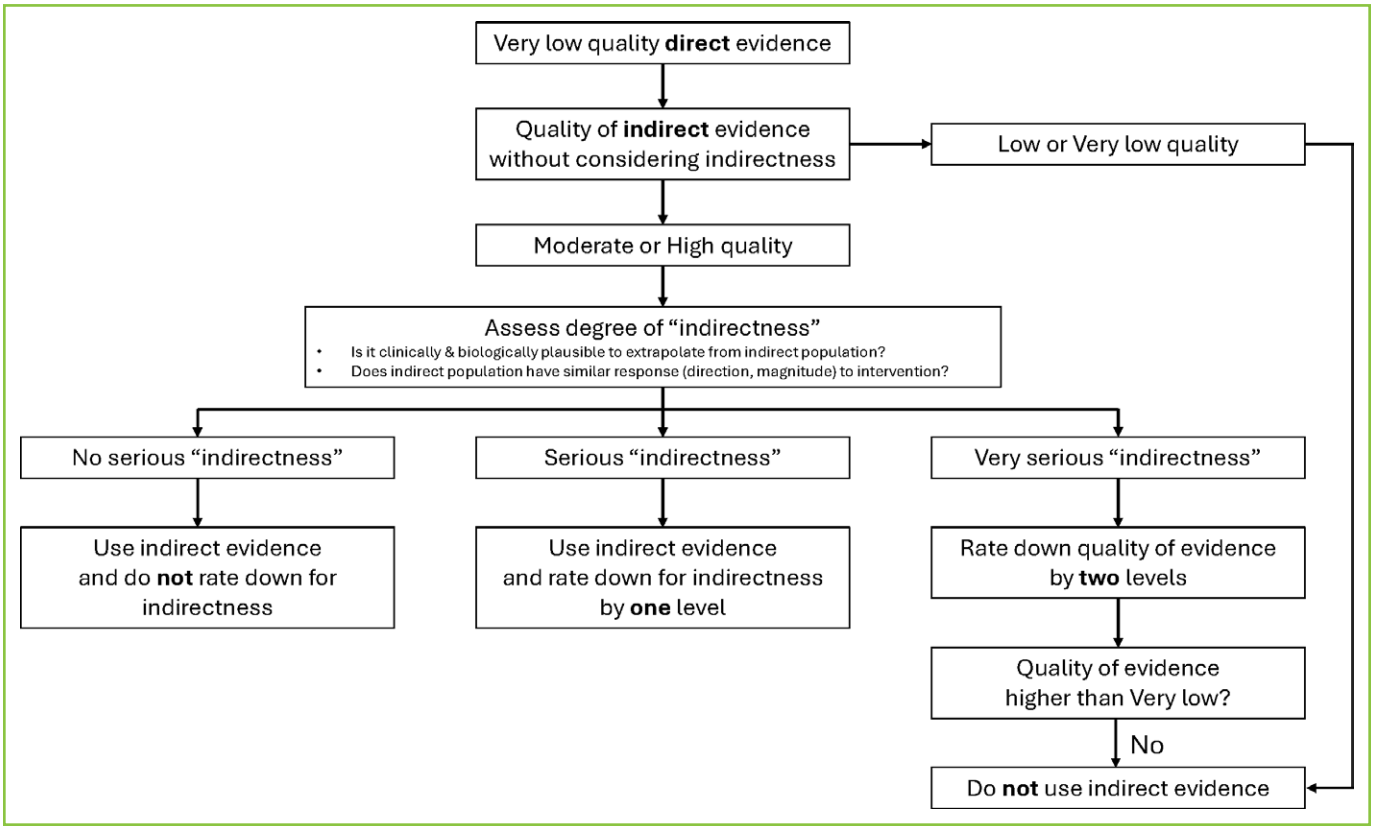
Very low quality **direct** evidence
Quality of **indirect** evidence without considering indirectness
Low or Very low quality
Moderate or High quality
Assess degree of "indirectness"
Is it clinically & biologically plausible to extrapolate from indirect population?
Does indirect population have similar response (direction, magnitude) to intervention?
No serious "indirectness"
Serious "indirectness"
Very serious "indirectness"
Use indirect evidence and do **not** rate down for indirectness
Use indirect evidence and rate down for indirectness by **one** level
Rate down quality of evidence by **two** levels
Quality of evidence higher than Very low?
No
Do **not** use indirect evidence

Figure 1. Framework to determine the appropriateness of using indirect evidence from studies of children without sepsis or from adults.

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Types of Recommendation Statements: Recommendations were specified as strong or conditional (previously referred to a "weak" recommendations in prior guidelines) as outlined in **Table 1**. We used the language "we recommend" for strong recommendations and "we suggest" for conditional recommendations. A strong recommendation indicates that most, if not all, individuals in the relevant clinical situation should receive (or avoid) the intervention. In contrast, a conditional recommendation acknowledges that the balance between desirable and undesirable may vary depending on patient values, clinical circumstances, or resource availability. Conditional recommendations may not be universally implementable and are less likely to be suitable for rigid performance metrics or enforcement. Flexibility and local context should guide their adaptation into policy.

In instances where there was insufficient evidence to formulate a recommendation, but the panel felt that some guidance based on current practice patterns may be appropriate, we issued an "in our practice" statement. The "in our practice" statements were developed through a survey of panelists to ascertain their state of current practice. As such, "in our practice" statements are intended only to describe current variation in care and are not meant to be construed as recommendations. Good practice statements (GPSs) were developed in accordance with GRADE guidance when the panel judged unequivocal benefit (or harm) was present but there was an absence of direct evidence (Table 1) (17).

Consensus Voting: All panel members convened to review evidence and discuss recommendations in three virtual meetings and subsequently voted on each recommendation to indicate agreement,

TABLE 1.
Types of Recommendation Statements and Implications of the Strength of Recommendation

Category	Strength	Certainty of Evidence	Implications to Patients	Implications to Clinicians	Implications to Policymakers
Strong recommendation	Strong	High or moderate	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Can be adapted as policy in most situations, including for use as performance indicators
Conditional recommendation[a]	Weak	Any	The majority of individuals in this situation would want the suggested course of action, but many would not	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances, such as patients' or family's values and preferences	Policies will likely be variable
Good practice statement	Strong	Ungraded	Same as strong recommendation	Same as strong recommendation	Same as strong recommendation
In our practice statement	Not a recommendation	NA	NA	NA	NA

NA = not applicable.

[a]Conditional recommendations were previously categorized as "weak recommendation" in prior guideline iterations.

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disagreement, or abstention. Only panel members without relevant conflicts of interest could vote. Up to three rounds of voting were conducted throughout this process of deliberation to achieve final consensus. Acceptance of a statement required votes from 75% of the panel members with an 80% agreement threshold.

Sepsis Terminology: In 2005, the International Pediatric Sepsis Consensus Conference (IPSCC) published definitions and criteria for sepsis, severe sepsis, and septic shock in children (18). In 2024, the SCCM Pediatric Sepsis Definitions Taskforce provided updated definitions and criteria. The resulting Phoenix criteria defined sepsis as infection with life-threatening organ dysfunction operationalized as moderate-severe dysfunction of the respiratory, cardiovascular, coagulation, and/or neurologic systems (19). Septic shock was operationalized as sepsis with at least 1 cardiovascular dysfunction point, indicating hypotension, hyperlactatemia greater than or equal to 5 mmol/L, and/or treatment with a vasoactive medication. However, the majority of studies used to establish evidence for both the 2020 guidelines and this update refer to the 2005 nomenclature in which severe sepsis was defined as: a) greater than or equal to 2 age-based systemic inflammatory response syndrome criteria, b) confirmed or suspected invasive infection, and c) cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or greater than or equal to 2 noncardiovascular organ system dysfunctions; and septic shock was defined as the subset with cardiovascular dysfunction, which included hypotension, impaired perfusion (including hyperlactatemia > 2 times the upper limit of normal), and/or treatment with a vasoactive medication (19). Therefore, for the purposes of this update, studies that used either the 2005 severe sepsis or septic shock criteria, the 2024 Phoenix sepsis or septic shock criteria, or a more general definition of severe infection leading to life-threatening organ dysfunction were included. Because several methods to identify acute organ dysfunction in children are available, including but not limited to the 2005 IPSCC and 2024 Phoenix sepsis criteria (19–25), we again chose not to require a specific definition or framework for this purpose.

The panel intended for these guidelines to apply to all patients with sepsis or septic shock from greater than or equal to 37 weeks gestation at birth to 18 years old. For this purpose, sepsis is defined as severe infection leading to life-threatening organ dysfunction, and septic shock is defined as a subset of sepsis that includes life-threatening cardiovascular dysfunction. Because the diagnosis of sepsis may be uncertain in clinical practice, we also incorporated standardized language for probable sepsis and suspected septic shock (**Table 2**). Practically, all infants, children, and adolescents with infections associated with acute organ dysfunction are included in this scope. For simplicity, we will henceforth use the term "children" to refer to infants, children, and adolescents in these guidelines.

All recommendations apply to children with sepsis or septic shock unless specific qualifications (e.g., subset with immune compromise) are included in the recommendation. Because sepsis exists as a spectrum, some children without known acute organ dysfunction may also benefit from similar therapies

TABLE 2.
Sepsis Terminology Used in These Guidelines

Term	Definition
Sepsis	Infection leading to life-threatening organ dysfunction, inclusive of patients with septic shock
Septic shock	Subset of sepsis with inadequate perfusion and/or cardiovascular dysfunction not attributable to a concurrent primary cardiac or other cause
Probable sepsis	Clinical presentation consistent with sepsis, but infection not yet confirmed
Suspected septic shock	Shock of unconfirmed etiology, but suspected to be secondary to infection
Septic shock with persistent hypoperfusion	Sepsis with ongoing signs of hypoperfusion despite initial treatment

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as those with known organ dysfunction. Finally, because medical care for children with sepsis and septic shock is carried out within the confines of locally available resources, the panel again supports that these guidelines should constitute a general scheme of care for translation to local treatment algorithms or bundles that account for variation in local healthcare determinants.

RESULTS

A summative guide for the initial resuscitation of children with probable sepsis or suspected septic shock is shown in **Figure 2**. A comparison of recommendations between the 2020 and 2026 guidelines is shown in **Table 3**.

A. RECOGNITION AND MANAGEMENT OF INFECTION

1. **In children who are acutely unwell, there was insufficient evidence to recommend implementing systematic sepsis screening, in addition to established clinical protocols, for the timely recognition of sepsis and septic shock.**

Change From 2020 Guidelines: Updated recommendation.

Rationale: Timely recognition of sepsis and septic shock in children is associated with faster interventions and improved patient outcomes based on biological rationale and observational studies. However, it remains unclear whether systematic screening for sepsis improves outcomes and, if so, which screening methods are most useful. While studies have reported on the diagnostic performance of various screening tools, ranging from paper-based to electronic medical record (EMR)-based approaches, most were conducted within well-established sepsis quality improvement initiatives rather than comparing use of a screening tool to identical control scenarios without screening (26–30). Across five observational studies, systematic screening for sepsis was not associated with mortality or hospital length of stay (LOS) (26–30). Furthermore, since the 2020 guidelines, the only pediatric study with randomized allocation to EMR-based sepsis screening or no screening was published which found no differences in mortality (relative risk [RR], 2.52; 95% CI, 0.31–20.38), the number of patients progressing to septic shock (adjusted odds ratio [OR], 1.12; 95% CI, 0.53–2.46), or antibiotic timeliness (adjusted hazard ratio [HR], 0.85; 95% CI, 0.63–1.16) (31). Because the overall balance of effects, with the incorporation of the new RCT, did not favor either systematic screening or the null alternative and the impact of systematic screening appears contingent on the institutional context/setting (e.g., hospital location, screening criteria and subsequent clinical response, additional sepsis triage, and treatment protocols), the panel was unable to issue a recommendation either for or against this intervention. However, the panel emphasizes the importance of: a) early recognition of children with sepsis or septic shock, b) a need for more robust comparative research to evaluate which tools augment early recognition in which settings, and c) establishing clinical protocols to triage and identify acutely unwell children within healthcare systems. The panel also acknowledged that the current body of evidence was largely based on electronic health record-based screening tools and that alternate approaches may be appropriate in different healthcare contexts.

2. **For children with sepsis or septic shock, we recommend that hospitals implement a performance improvement program, including standard operating procedures for treatment (strong recommendation, low certainty of evidence).**

Change From 2020 Guidelines: Updated recommendation.

Rationale: Cornerstones of optimal care include standardizing the recognition and clinical management of children with sepsis and septic shock through institutional protocols, providing education to healthcare professionals to ensure reliable local implementation, and conducting regular performance audits (3). Implementation of a sepsis performance improvement program has been associated with reduced mortality (RR, 0.51; 95% CI, 0.39–0.66) and shorter hospital LOS (mean difference [MD], 0.87 d; 95% CI, 1.66 fewer to 0.08 fewer days) in observational studies (26, 32–43). In addition, implementation of a clinical pathway for sepsis management as one component of that performance improvement program has also been associated with reduced mortality (RR, 0.61; 95% CI, 0.39–0.95) and shorter hospital LOS (MD, 36.71 hr; 95% CI, 70.33 to 3.09 fewer hours) (38). Most studies have focused on timely interventions, such as obtaining blood cultures and/or administering antibiotics,

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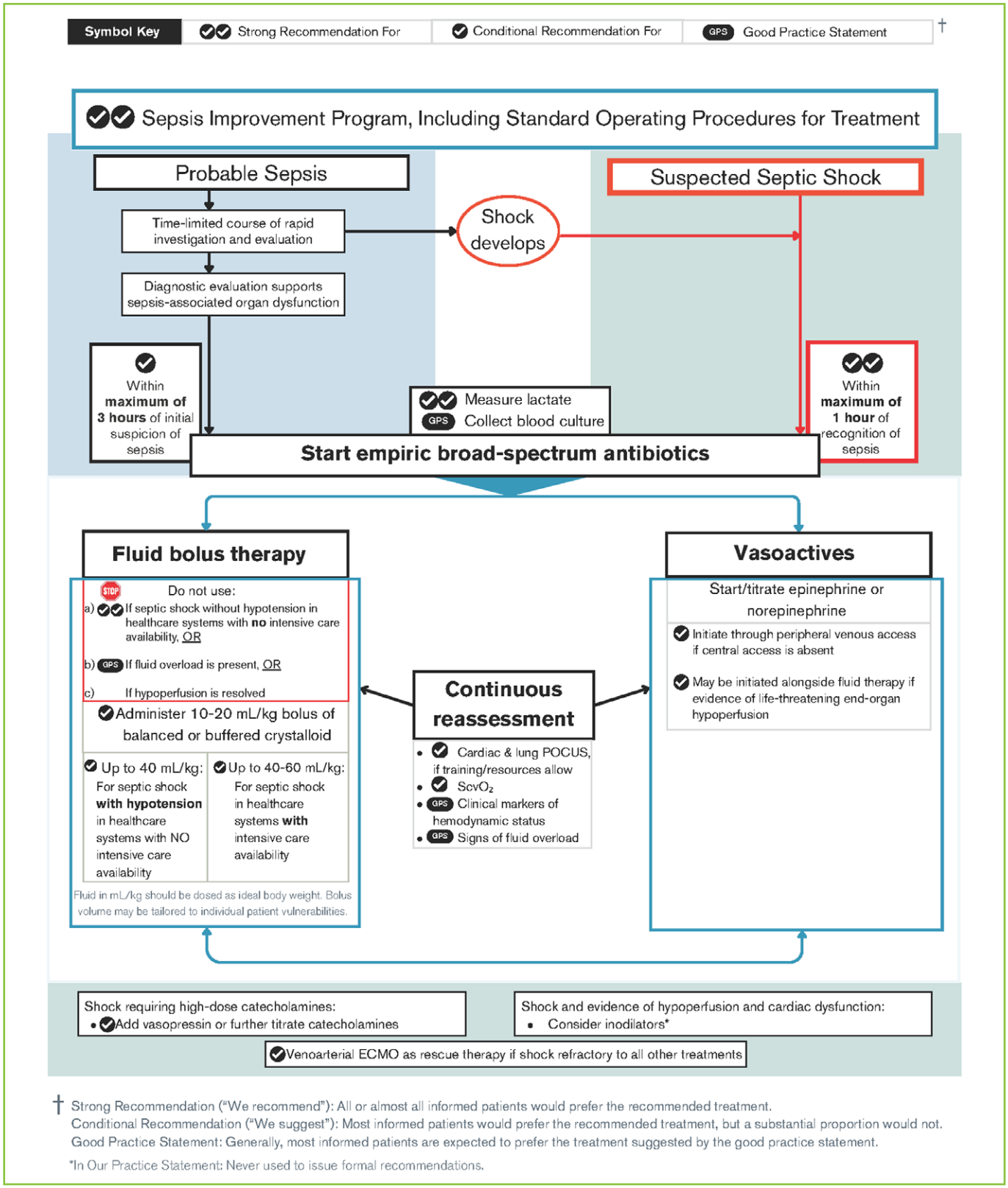
Symbol Key
Strong Recommendation For
Conditional Recommendation For
GPS Good Practice Statement
†
Sepsis Improvement Program, Including Standard Operating Procedures for Treatment
Probable Sepsis
Time-limited course of rapid investigation and evaluation
Diagnostic evaluation supports sepsis-associated organ dysfunction
Shock develops
Suspected Septic Shock
Within maximum of 3 hours of initial suspicion of sepsis
Measure lactate
GPS Collect blood culture
Within maximum of 1 hour of recognition of sepsis
Start empiric broad-spectrum antibiotics
Fluid bolus therapy
STOP Do not use:
a) If septic shock without hypotension in healthcare systems with no intensive care availability, OR
b) GPS If fluid overload is present, OR
c) If hypoperfusion is resolved
Administer 10-20 mL/kg bolus of balanced or buffered crystalloid
Up to 40 mL/kg: For septic shock with hypotension in healthcare systems with NO intensive care availability
Up to 40-60 mL/kg: For septic shock in healthcare systems with intensive care availability
Fluid in mL/kg should be dosed as ideal body weight. Bolus volume may be tailored to individual patient vulnerabilities.
Continuous reassessment
Cardiac & lung POCUS, if training/resources allow
ScvO2
GPS Clinical markers of hemodynamic status
GPS Signs of fluid overload
Vasoactives
Start/titrate epinephrine or norepinephrine
Initiate through peripheral venous access if central access is absent
May be initiated alongside fluid therapy if evidence of life-threatening end-organ hypoperfusion
Shock requiring high-dose catecholamines:
Add vasopressin or further titrate catecholamines
Shock and evidence of hypoperfusion and cardiac dysfunction:
Consider inodilators*
Venoarterial ECMO as rescue therapy if shock refractory to all other treatments
† Strong Recommendation ("We recommend"): All or almost all informed patients would prefer the recommended treatment.
Conditional Recommendation ("We suggest"): Most informed patients would prefer the recommended treatment, but a substantial proportion would not.
Good Practice Statement: Generally, most informed patients are expected to prefer the treatment suggested by the good practice statement.
*In Our Practice Statement: Never used to issue formal recommendations.

Figure 2. Quick guide for initial resuscitation in children with probable sepsis without shock or suspected septic shock. A summary of key recommendations for recognition and resuscitation with indications of the strength of recommendations. Fluid bolus therapy and vasoactive administration should be continuously reassessed. ECMO = extracorporeal membrane oxygenation, GPS = good practice statement, POCUS = point-of-care ultrasound, $Scvo_2$ = central venous oxygen saturation.

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TABLE 3.
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
A. Screening, Diagnosis, and Systematic Management of Sepsis	**A. Recognition and Management of Infection**	
1. In children who present as acutely unwell, we suggest implementing systematic screening for timely recognition of septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence). **Remark**: Systematic screening needs to be tailored to the type of patients, resources, and procedures within each institution. Evaluation for the effectiveness and sustainability of screening should be incorporated as part of this process.	1. In children who are acutely unwell, there was insufficient evidence to recommend implementing systematic sepsis screening, in addition to established clinical protocols, for the timely recognition of sepsis and septic shock.	Updated
2. We were unable to issue a recommendation about using blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction into low- vs. high-risk of having septic shock or sepsis.	3. For children with probable sepsis or suspected septic shock, we recommend measuring blood lactate as part of initial evaluation and management (strong recommendation, very low certainty evidence).	Updated
3. We *recommend* implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction (BPS).	2. For children with sepsis or septic shock, we recommend that hospitals implement a performance improvement program, including standard operating procedures for treatment (strong recommendation, low certainty of evidence).	Updated
4. We *recommend* obtaining blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (BPS).	4. Clinicians should obtain blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (GPS).	No change, carried over
	5. For children with probable sepsis or suspected/confirmed septic shock, there was insufficient evidence to issue a recommendation for or against routine molecular testing for pathogen detection or identification.	New
B. Antimicrobial Therapy		
5. In children with septic shock, we *recommend* starting antimicrobial therapy as soon as possible, within 1 hr of recognition (strong recommendation, very low quality of evidence).	6. For children with suspected septic shock, we recommend starting antimicrobial therapy as soon as possible, ideally within 1 hr of recognition of sepsis (strong recommendation, very low certainty of evidence).	Updated
6. In children with sepsis-associated organ dysfunction but without shock, we suggest starting antimicrobial therapy *as soon as possible* after appropriate evaluation, within 3 hr of recognition (weak recommendation, very low quality of evidence).	7. For children with probable sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for sepsis is substantiated, starting antimicrobial therapy as soon as possible after appropriate evaluation, ideally within 3 hr of recognition (conditional recommendation, very low certainty of evidence).	Updated

(*Continued*)

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
	8. For children with probable bacterial sepsis, where timely evaluation is difficult and there may be a delay due to other issues in clinical care, clinicians should consider giving antibiotics as soon as possible (GPS).	Updated
7. We *recommend* empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (BPS).	9. Clinicians should administer empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (GPS).	No change, carried over
8. Once the pathogen(s) and sensitivities are available, we *recommend* narrowing empiric antimicrobial therapy coverage (BPS).	12. Once the pathogen(s) and susceptibilities are available, empiric antimicrobial therapy coverage should be narrowed (GPS).	No change, carried over
9. If no pathogen is identified, we *recommend* narrowing or stopping empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice (BPS).	13. If no pathogen is identified, clinicians should narrow or stop empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice (GPS).	No change, carried over
10. In children without immune compromise and without high risk for multidrug-resistant pathogens, we *suggest* against the routine use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy (weak recommendation, very low quality of evidence). **Remark**: In certain situations, such as confirmed or strongly suspected group B streptococcal sepsis, use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy may be indicated.		2020 recommendation not reviewed
11. In children with immune compromise and/or at high risk for multidrug-resistant pathogens, we *suggest* using empiric multidrug therapy when septic shock or other sepsis-associated organ dysfunction is present/suspected (weak recommendation, very low quality of evidence).	10. For children treated for sepsis or septic shock with immune compromise and/or are at high risk for multidrug-resistant pathogens, we suggest using empiric multidrug therapy (conditional recommendation, very low certainty of evidence).	No change, carried over
12. We *recommend* using antimicrobial dosing strategies that have been optimized based on published pharmacokinetic/pharmacodynamic principles and with consideration of specific drug properties (BPS).		2020 recommendation not reviewed
	11. For children with confirmed bacterial sepsis being treated with beta-lactam antibiotics, there was insufficient evidence to recommend for or against routinely using a continuous and/or extended infusion strategy, compared with intermittent dosing.	New

(*Continued*)

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
13. In children with septic shock or sepsis-associated organ dysfunction who are receiving antimicrobials, we *recommend* daily assessment (e.g., clinical, laboratory assessment) for de-escalation of antimicrobial therapy (BPS). **Remark**: This assessment should include a review of the ongoing indication for empiric antimicrobial therapy after the first 48 hr, i.e., guided by microbiologic results and in response to clinical improvement and/or evidence of infection resolution. This recommendation applies to patients being treated with empiric, targeted, and combination therapy.		2020 recommendation not reviewed
14. We *recommend* determining the duration of antimicrobial therapy according to the site of infection, microbial etiology, response to treatment, and ability to achieve source control (BPS).		2020 recommendation not reviewed
	14. For children with sepsis or septic shock treated with antimicrobial therapy, we suggest not using procalcitonin routinely to guide de-escalation of therapy when effective antimicrobial stewardship programs are in place (conditional recommendation, moderate certainty of evidence).	New
	15. For children with sepsis or septic shock *with* documented bloodstream infection, we suggest hospitals implement routine infectious diseases or medical microbiology consultation for management advice (conditional recommendation, very low certainty of evidence).	New
	16. For children with sepsis or septic shock *without* documented bloodstream infection, there was insufficient evidence to provide a recommendation about whether hospitals should implement routine infectious diseases consultation.	New
C. Source Control		
15. We *recommend* that emergent source control intervention be implemented as soon possible after a diagnosis of an infection amenable to a source control procedure is made (BPS). **Remark**: Appropriate diagnostic testing to identify the site of infection and microbial etiology should be performed, and advice from specialist teams (e.g., infectious diseases, surgery) should be sought, as appropriate, in order to prioritize interventions needed to achieve source control.	17. Emergent source control intervention should be implemented as soon as possible after a diagnosis of an infection amenable to a source control procedure (GPS).	No change, carried over

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
16. We *recommend* removal of intravascular access devices that are confirmed to be the source of sepsis or septic shock after other vascular access has been established and depending on the pathogen and the risks/benefits of a surgical procedure (strong recommendation, low quality of evidence).	18. For children with sepsis or septic shock, we recommend removal of intravascular access devices that are confirmed to be the source of sepsis or septic shock after other vascular access has been established and depending on the pathogen and the risks/benefits of a surgical procedure (strong recommendation, low certainty of evidence).	No change, carried over
D. Fluid Therapy		
17. In healthcare systems with availability of intensive care, we *suggest* administering up to 40–60 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).	19. For children with septic shock being treated in healthcare systems with intensive care availability, we suggest administering up to 40–60 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour of initial resuscitation, over no fluid bolus (conditional recommendation, low certainty evidence).	No change, carried over
18. In healthcare systems with no availability of intensive care and *in the absence of hypotension*, we recommend against bolus fluid administration while starting maintenance fluids (strong recommendation, high quality of evidence).	20. For children with sepsis *without hypotension* being treated in healthcare systems with no intensive care availability, we recommend against using fluid bolus therapy, while starting maintenance fluids (strong recommendation, high certainty evidence).	No change, carried over
19. In healthcare systems with no availability of intensive care, *if hypotension is present*, we suggest administering up to 40 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour with titration to clinical markers of cardiac output and discontinued if signs of fluid overload develop (weak recommendation, low quality of evidence). **Remark**: Clinical markers of cardiac output may include heart rate, blood pressure, capillary refill time, level of consciousness, and urine output. In all settings, the need for fluid administration should be guided by frequent reassessment of clinical markers of cardiac output, serial blood lactate measurement, and advanced monitoring, when available. Signs of fluid overload that should limit further fluid bolus therapy may include clinical signs of pulmonary edema or new or worsening hepatomegaly.	21. For children with septic shock *with hypotension* being treated in healthcare systems with no intensive care availability, we suggest administering up to 40 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour of initial resuscitation over no fluid bolus therapy (conditional recommendation, low certainty evidence).	No change, carried over

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
	22. Hemodynamic status should be reassessed after every fluid bolus. Fluid bolus therapy should be titrated to clinical markers of cardiac output and discontinued if shock resolves or if signs of fluid overload develop (GPS).	No change, carried over (from 2020 remarks)
20. We *suggest* using crystalloids, rather than albumin, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence). **Remark**: Although there is no difference in outcomes, this recommendation takes into consideration cost and other barriers of administering albumin compared with crystalloids.	23. For the initial resuscitation of children with sepsis or septic shock, we suggest using crystalloids, rather than albumin (conditional recommendation, moderate certainty of evidence).	No change, carried over
21. We *suggest* using balanced/buffered crystalloids, rather than 0.9% saline, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).	24. For children with septic shock requiring treatment with fluid boluses, we suggest resuscitation with balanced or buffered crystalloid solutions over 0.9% saline (conditional recommendation, very low certainty of evidence).	No change after review
22. We *recommend* against using starches in the acute resuscitation of children with septic shock or other sepsis-associated organ dysfunction (strong recommendation, moderate quality of evidence).		2020 recommendation not reviewed
23. We *suggest* against using gelatin in the resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).		2020 recommendation not reviewed
E. Hemodynamic Monitoring		
	25. Resuscitation for children with sepsis or septic shock should be guided by ongoing clinical assessment of markers of hemodynamic status, including heart rate, blood pressure, capillary refill time, extremity temperature, pulse quality, level of consciousness, and urine output (GPS).	New
24. We were unable to issue a recommendation about whether to target MAP at the fifth or 50th percentile for age in children with septic shock and other sepsis-associated organ dysfunction.	26. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation about whether to target MAP at the 5th or 50th percentile for age.	No change, carried over
25. We *suggest* not using bedside clinical signs in isolation to categorize septic shock in children as "warm" or "cold" (weak recommendation, very low quality of evidence).		2020 recommendation not reviewed

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
26. We *suggest* using advanced hemodynamic variables, when available, in addition to bedside clinical variables to guide the resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). **Remark**: Advanced hemodynamic monitoring may include cardiac output/cardiac index, systemic vascular resistance, or $Scvo_2$.	27. For children with septic shock, we suggest targeting $Scvo_2 \geq 70\%$ when central venous access is available, over not targeting $Scvo_2$ (conditional recommendation, very low certainty evidence).	Updated
	28. For children with sepsis and septic shock, there was insufficient evidence to issue a recommendation on use of advanced hemodynamic monitoring along with bedside clinical signs to guide resuscitation.	Updated
	29. For children with sepsis or septic shock, we suggest using cardiac and lung POCUS to guide resuscitation, over not using POCUS to guide resuscitation, if local training and resources allow (conditional recommendation, low certainty evidence).	New
27. We *suggest* using trends in blood lactate levels, in addition to clinical assessment, to guide resuscitation of children with septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence). **Remark**: In children with an elevated blood lactate, repeat testing that reveals a persistent elevation in blood lactate may indicate incomplete hemodynamic resuscitation and should prompt efforts, as needed, to further promote hemodynamic stability.		2020 recommendation incorporated into 2026 recommendation 3
F. Vasoactive Medications		
	30. For children with septic shock, there was insufficient evidence to issue a recommendation on initiating vasoactive medications either before or after 40 mL/kg of bolus fluid therapy (conditional recommendation, very low certainty of evidence).	New
28. We *suggest* using epinephrine, rather than dopamine, in children with septic shock (weak recommendation, low quality of evidence). 29. We *suggest* using norepinephrine, rather than dopamine, in children with septic shock (weak recommendation, very low quality of evidence). 30. We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock.	31. For children with septic shock requiring vasoactive medications, there was insufficient evidence to issue a recommendation on the preferred use of epinephrine or norepinephrine for first-line therapy in children with septic shock.	Updated

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
31. We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock. **Remark**: It is reasonable to begin vasoactive infusions after 40–60 mL/kg of fluid resuscitation if the patient continues to have evidence of abnormal perfusion. Either epinephrine or norepinephrine may be administered through a peripheral vein (or intraosseous, if in place) if central venous access is not readily accessible. Dopamine may be substituted as the first-line vasoactive infusion, administered either peripherally or centrally, if epinephrine or norepinephrine is not readily available.	32. For children with septic shock requiring vasoactive medications, we suggest initiating vasoactive medications through peripheral venous access over delaying therapy until central venous access is obtained (conditional recommendation, very low certainty of evidence).	Updated
32. We *suggest* either adding vasopressin or further titrating catecholamines in children with septic shock who require high-dose catecholamines (weak recommendation, low quality of evidence). **Remark**: No consensus was achieved on the optimal threshold for initiating vasopressin. Therefore, this decision should be made according to individual clinician preference.	33. For children with septic shock who require high-dose catecholamines, we suggest either adding vasopressin or further titrating catecholamines (conditional recommendation, low certainty of evidence).	No change, carried over
33. We were unable to issue a recommendation about adding an inodilator in children with septic shock and cardiac dysfunction despite other vasoactive agents.	34. For children with septic shock and cardiac dysfunction despite treatment with initial vasoactive medications, there was insufficient evidence to issue a recommendation about adding an inodilator.	No change, carried over
	35. For children with septic shock with persistent hypoperfusion despite treatment with other vasoactive medications, there was insufficient evidence to issue a recommendation for co-treatment with angiotensin II.	New
	36. For children with septic shock with persistent hypoperfusion despite treatment with other vasoactive medications, there was insufficient evidence to issue a recommendation for co-treatment with methylene blue.	New
G. Ventilation		
34. We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock.	37. For children with fluid-refractory, catecholamine-resistant septic shock, there was insufficient evidence to issue a recommendation about whether to intubate in the absence of respiratory failure.	No change, carried over
35. We *suggest* not to use etomidate when intubating children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).	38. For children with sepsis or septic shock, we suggest against using etomidate when intubating (conditional recommendation, low certainty of evidence).	No change, carried over

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
	39. For intubated children with sepsis or septic shock following resuscitation, we suggest titrating supplemental oxygen to target a conservative range (Spo_2 88–92%) over a more liberal target (Spo_2 > 94%; conditional recommendation, moderate certainty of evidence).	New
36. We *suggest* a trial of noninvasive mechanical ventilation (over invasive mechanical ventilation) in children with sepsis-induced PARDS without a clear indication for intubation and who are responding to initial resuscitation (weak recommendation, very low quality of evidence). **Remark**: When noninvasive mechanical ventilation is initiated, clinicians should carefully and frequently reevaluate the patient's condition.		2020 recommendation not reviewed; now defer to other guidelines
37. We *suggest* using high PEEP in children with sepsis-induced PARDS (weak recommendation, very low quality of evidence). **Remark**: The exact level of high PEEP has not been tested or determined in PARDS patients. Some RCTs and observational studies in PARDS have used and advocated for use of the ARDS-network PEEP to Fio_2 grid, although adverse hemodynamic effects of high PEEP may be more prominent in children with septic shock.		2020 recommendation not reviewed; now defer to other guidelines
38. We *cannot suggest* for or against the use of recruitment maneuvers in children with sepsis-induced PARDS and refractory hypoxemia. **Remark**: If a recruitment maneuver is considered, the use of a stepwise, incremental and decremental PEEP titration maneuver is preferred over sustained inflation techniques that have not been optimized through direct testing in PARDS patients. All PARDS patients must be carefully monitored for tolerance of the maneuver.		2020 recommendation not reviewed; now defer to other guidelines
39. We *suggest* a trial of prone positioning in children with sepsis and severe PARDS (weak recommendation, low quality of evidence). **Remark**: Research trials in adults with ARDS and children with PARDS have emphasized prone positioning for at least 12 hr/d, as tolerated.		2020 recommendation not reviewed; now defer to other guidelines

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
40. We *recommend* against the routine use of iNO in all children with sepsis-induced PARDS (strong recommendation, low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
41. We *suggest* using iNO as a rescue therapy in children with sepsis-induced PARDS and refractory hypoxemia after other oxygenation strategies have been optimized (weak recommendation, moderate quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
42. We were unable to issue a recommendation to use high-frequency oscillatory ventilation vs. conventional ventilation in children with sepsis-induced PARDS.		2020 recommendation not reviewed; now defer to other guidelines
43. We *suggest* using neuromuscular blockade in children with sepsis and severe PARDS (weak recommendation, very low quality of evidence). **Remark**: The exact duration of neuromuscular blockade use in severe PARDS patients has not been determined to date. Most of the adult RCT data and pediatric observational data support treatment for 24–48 hr after ARDS onset.		2020 recommendation not reviewed; now defer to other guidelines
H. Corticosteroids		
44. We *suggest* against using IV hydrocortisone to treat children with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (weak recommendation, low quality of evidence).	40. For children with septic shock in whom hemodynamic stability can be restored with fluid resuscitation and vasoactive therapy, we suggest against the use of IV hydrocortisone (conditional recommendation, low certainty of evidence).	No change after review
45. We *suggest* that either IV hydrocortisone or no hydrocortisone may be used if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability (weak recommendation, low quality of evidence).	41. For children with septic shock who remain hemodynamically unstable despite adequate fluid resuscitation and vasoactive therapy, there was insufficient evidence to issue a recommendation on whether to treat with IV hydrocortisone. **Remark**: Although routine use of corticosteroids in children with sepsis or septic shock is not recommended, stress-dose corticosteroids should be administered for suspected or documented adrenal insufficiency.	Updated
I. Endocrine and Metabolic		
46. We *recommend* against insulin therapy to maintain glucose target at or below 140 mg/dL (7.8 mmol/L; strong recommendation, moderate quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
47. We were unable to issue a recommendation regarding what blood glucose range to target for children with septic shock and other sepsis-associated organ dysfunction.		2020 recommendation not reviewed; now defer to other guidelines
	43. For children with sepsis or septic shock and metabolic acidemia, there was insufficient evidence to issue a recommendation on the use of sodium bicarbonate.	New
48. We were unable to issue a recommendation as to whether to target normal blood calcium levels in children with septic shock or sepsis-associated organ dysfunction.	44. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation about whether to target normal blood calcium levels or tolerate hypocalcemia.	No change, carried over
49. We *suggest* against the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state (weak recommendation, low quality of evidence).	45. For children with sepsis or septic shock in a sick euthyroid state, we suggest against the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction (conditional recommendation, low certainty of evidence).	No change, carried over
50. We *suggest* either antipyretic therapy or a permissive approach to fever in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).	42. For children with sepsis or septic shock with fever, there was insufficient evidence to issue a recommendation on whether to target normothermia or take a permissive approach to fever.	Updated
J. Nutrition		
51. We were unable to issue a recommendation regarding early hypocaloric/trophic enteral feeding followed by slow increase to full enteral feeding vs. early full enteral feeding in children with septic shock or sepsis-associated organ dysfunction without contraindications to enteral feeding.		2020 recommendation not reviewed; now defer to other guidelines
52. We *suggest* not withholding enteral feeding solely on the basis of vasoactive-inotropic medication administration (weak recommendation, low quality of evidence). **Remark**: Enteral feeding is not contraindicated in children with septic shock after adequate hemodynamic resuscitation who no longer require escalating doses of vasoactive agents or in whom weaning of vasoactive agents has started.		2020 recommendation not reviewed; now defer to other guidelines

(*Continued*)

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
53. We *suggest* enteral nutrition as the preferred method of feeding and that parenteral nutrition may be withheld in the first 7 d of PICU admission in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
54. We *suggest* against supplementation with specialized lipid emulsions in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
55. We *suggest* against the routine measurements of gastric residual volumes in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
56. We *suggest* administering enteral feeds through a gastric tube, rather than a post-pyloric feeding tube, to children with septic shock or other sepsis-associated organ dysfunction who have no contraindications to enteral feeding (weak recommendation, low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
57. We *suggest* against the routine use of prokinetic agents for the treatment of feeding intolerance in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
58. We *suggest* against the use of selenium in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
59. We *suggest* against the use of glutamine supplementation in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
60. We *suggest* against the use of arginine in the treatment of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines
61. We *suggest* against using zinc supplementation in children with septic shock and other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
62. We *suggest* against the use of ascorbic acid (vitamin C) in the treatment of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).	46. For children with sepsis or septic shock, we suggest against the use of vitamin C (ascorbic acid; conditional recommendation, very low certainty evidence).	No change after review
63. We *suggest* against the use of thiamine to treat children with sepsis-associated organ dysfunction (weak recommendation, low quality of evidence).	47. For children with sepsis or septic shock, we suggest against the use of thiamine (vitamin B1; conditional recommendation, very low certainty evidence).	No change after review
64. We *suggest* against the acute repletion of vitamin D deficiency for treatment of septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).	48. For children with sepsis or septic shock, we suggest against the acute repletion of vitamin D in the absence of clinical vitamin D insufficiency (conditional recommendation, very low certainty of evidence).	No change, carried over
K. Blood Products		
65. We *suggest* against transfusion of RBCs if the blood hemoglobin concentration is ≥ 7 g/dL in hemodynamically stabilized children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). **Remark**: According to the 2018 Transfusion and Anemia Expertise Initiative guidelines, for the purposes of RBC transfusion, "hemodynamically stabilized" is defined as a MAP higher than 2 SDs below normal for age and no increase in vasoactive medications for at least 2 hr.		2020 recommendation not reviewed; now defer to other guidelines
66. We cannot make a recommendation regarding hemoglobin transfusion thresholds for critically ill children with unstable septic shock.		2020 recommendation not reviewed; now defer to other guidelines
67. We *suggest* against prophylactic platelet transfusion based solely on platelet levels in nonbleeding children with septic shock or other sepsis-associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence).		2020 recommendation not reviewed; now defer to other guidelines

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
68. We *suggest* against prophylactic plasma transfusion in nonbleeding children with septic shock or other sepsis-associated organ dysfunction and coagulation abnormalities (weak recommendation, very low quality of evidence). **Remark**: Prophylactic plasma transfusion refers to situations in which there is an abnormality in laboratory coagulation testing but no active bleeding.		2020 recommendation not reviewed; now defer to other guidelines
L. Plasma Exchange, Renal Replacement, and Extracorporeal Support	**L. Fluid Balance, Renal Replacement, and Extracorporeal Support**	
69. We *suggest* against using plasma exchange in children with septic shock or other sepsis-associated organ dysfunction without TAMOF (weak recommendation, very low quality of evidence).		2020 recommendation not reviewed
70. We cannot suggest for or against the use of plasma exchange in children with septic shock or other-sepsis-associated organ dysfunction with TAMOF.	51. For children with sepsis or septic shock who meet criteria for the TAMOF subphenotype, there was insufficient evidence to issue a recommendation on whether to treat with plasma exchange.	No change after review
	52. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation on the use of extracorporeal blood purification.	New
	49. It is reasonable to consider measures to prevent excessive fluid administration, monitor total fluid intake, and consider active fluid removal in case of fluid overload after hemodynamic stability is achieved and while closely monitoring hemodynamic changes to avoid compromising end-organ perfusion (GPS).	New
71. We *suggest* using renal replacement therapy to prevent or treat fluid overload in children with septic shock or other sepsis-associated organ dysfunction who are unresponsive to fluid restriction and diuretic therapy (weak recommendation, very low quality of evidence).		2020 recommendation incorporated into 2026 recommendation 49
72. We *suggest* against high-volume hemofiltration over standard hemofiltration in children with septic shock or other sepsis-associated organ dysfunction who are treated with renal replacement therapy (weak recommendation, low quality of evidence).	50. For children with sepsis or septic shock requiring renal replacement therapy, we suggest using high-volume hemofiltration (> 35 mL/kg/hr) over standard-volume hemofiltration (≤ 35 mL/kg/hr; conditional recommendation, low certainty of evidence).	Updated

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
73. We *suggest* using venovenous ECMO in children with sepsis-induced PARDS and refractory hypoxia (weak recommendation, very low quality of evidence).	53. For children with sepsis or septic shock, we suggest using venovenous ECMO when refractory hypoxia is present despite other therapies (conditional recommendation, very low certainty of evidence).	No change, carried over
74. We *suggest* using venoarterial ECMO as a rescue therapy in children with septic shock only if refractory to all other treatments (weak recommendation, very low quality of evidence).	54. For children with septic shock, we suggest using venoarterial ECMO as a rescue therapy only if shock is refractory to all other treatments (conditional recommendation, very low certainty of evidence).	No change, carried over
M. Immunoglobulins	**M. Immune Therapies**	
	55. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation on whether to taper or discontinue immunosuppressive therapies.	New
75. We *suggest* against the routine use of IVIG in children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). **Remark**: Although routine use of IVIG is not recommended, select patients may benefit from such treatment.	56. For children with sepsis or septic shock, we suggest against the routine use of IVIG (conditional recommendation, low certainty of evidence). **Remark**: The routine use of IVIG is not recommended. However, select patients, such as those with primary humoral immunodeficiencies or immunocompromising comorbidities with documented low immunoglobulin levels, may benefit from such treatment.	No change after review
	57. For children with sepsis or septic shock with evidence of leukopenia or immunoparalysis, there was insufficient evidence to issue a recommendation on the use of an immune stimulant.	New
	58. For children with sepsis or septic shock and hyperferritinemia, there was insufficient evidence to issue a recommendation on the use of immunosuppressive therapies.	New
N. Prophylaxis	**N. Long-Term Follow-Up**	
76. We *suggest* against the routine use of stress ulcer prophylaxis in critically ill children with septic shock or other sepsis-associated organ dysfunction, except for high-risk patients (weak recommendation, very low quality of evidence). **Remark**: Although *routine* stress ulcer prophylaxis is not recommended, some high-risk patients may benefit from stress ulcer prophylaxis. Studies have supported benefit of stress ulcer prophylaxis when baseline rate of clinically important bleeding is approximately 13%.		2020 recommendation not reviewed

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TABLE 3. (*Continued*)
Comparison of 2020 and 2026 Recommendations

2020 Recommendation	2026 Recommendation	Change From 2020 to 2026
77. We *suggest* against routine deep vein thrombosis prophylaxis (mechanical or pharmacologic) in critically ill children with septic shock or other sepsis-associated organ dysfunction, but potential benefits may outweigh risks and costs in specific populations (weak recommendation, low quality of evidence).		2020 recommendation not reviewed
	59. For children with sepsis or septic shock, we suggest implementing an individualized, early rehabilitation bundle during the acute illness rather than not using a rehabilitation bundle (conditional recommendation, very low certainty evidence).	New
	60. For children with sepsis or septic shock, there was insufficient evidence to recommend for or against targeted post-hospital follow-up.	New
	61. For children who survive sepsis or septic shock, it is reasonable to: 1) assess risk factors for post-sepsis morbidity, 2) educate the patient, family, and clinicians on the symptoms of post-sepsis morbidity, and 3) evaluate for new, long-term sequelae after hospital discharge (GPS).	New

ARDS = acute respiratory distress syndrome, BPS = best practice statement, ECMO = extracorporeal membrane oxygenation, GPS = good practice statement, iNO = inhaled nitric oxide, IVIG = IV immunoglobulin, MAP = mean arterial blood pressure, PARDS = pediatric acute respiratory distress syndrome, PEEP = positive end-expiratory pressure, POCUS = point-of-care ultrasound, RCT = randomized controlled trial, $Scvo_2$ = central venous oxygen saturation, Spo_2 = peripheral oxygen saturation, TAMOF = thrombocytopenia-associated multiple organ failure.

but these are usually administered as part of larger bundles of care and embedded within wider quality improvement programs that also include early recognition of sepsis (38, 44, 45). No studies have directly compared different bundles or pathways, and the available observational data do not permit discrimination of the effect of specific bundle components. However, given overall consistency across observational studies along with desirable effects and high feasibility for implementation across diverse health systems, the panel issued a strong recommendation that hospitals implement a performance improvement program, including standard operating procedures for treatment. Ideally, performance improvement programs should be adapted for and driven by local needs along with regular auditing and optimization with a particular focus on appropriate use of antibiotics (46). Future research should delineate which components of these bundled interventions are of highest value and how best to implement performance improvement across diverse healthcare systems.

3. **For children with probable sepsis or suspected septic shock, we recommend measuring blood lactate as part of initial evaluation and management (strong recommendation, very low certainty evidence).**

Change From 2020 Guidelines: Updated recommendation.

Rationale: Blood lactate levels are an indirect and nonspecific marker of global tissue perfusion and raised levels (≥ 2 mmol/L) are independently associated with increased mortality. The association of hyperlactatemia from arterial, venous, and capillary blood samples with mortality has been reported consistently across observational studies (47, 48). Lactate was also

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confirmed as one of three possible criteria (hyperlactatemia, hypotension, vasoactive medications) used to operationalize septic shock in the Phoenix criteria (19). Thus, blood lactate should be measured as part of the assessment of children with probable sepsis or suspected septic shock. While a lactate level greater than 5 mmol/L is sufficient to meet criteria for cardiovascular dysfunction in the Phoenix criteria (19), even smaller increases in blood lactate may indicate insufficient organ perfusion and justify initiating treatment for septic shock (47, 49). Although there are no interventional studies testing the impact of measuring blood lactate on clinical outcomes in children, a network meta-analysis of two RCTs in adults with sepsis or septic shock demonstrated that lactate-guided therapy was associated with lower short-term mortality up to 90 days compared with usual care (RR, 0.59; 95% CI, 0.45–0.76) (50). Furthermore, observational studies have shown a consistent association of blood lactate with risk of mortality (47, 51). The potential undesirable effects (e.g., pain with blood collection) of lactate measurement are comparably trivial, and there is a need to ensure availability of point-of-care lactate testing in diverse regions around the world. Thus, the panel issued a strong recommendation to measure blood lactate as part of initial evaluation and management of probable sepsis or suspected septic shock. Further research in children should focus on how best to integrate initial and serial lactate measurements into ongoing sepsis resuscitation.

4. **Clinicians should obtain blood cultures before initiating antimicrobial therapy in situations where this does not substantially delay antimicrobial administration (GPS).**

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

5. **For children with probable sepsis or suspected/confirmed septic shock, there was insufficient evidence to issue a recommendation for or against routine molecular testing for pathogen detection or identification.**

Change From 2020 Guidelines: New recommendation.

Rationale: Recent advances in molecular testing offer increasing possibilities for rapid and sensitive detection of microbial pathogens and antimicrobial resistance patterns. The theoretical benefits to identify and risk-stratify children with probable sepsis through such rapid and sensitive identification of causative pathogens hold promise for targeted antimicrobial treatment and streamlined clinical management. Currently, available molecular testing platforms range from blood-based (or other biologic fluids) molecular tests that can identify microbes before traditional blood culture methods to rapid speciation of cultured pathogens with or without information about molecular-based antimicrobial resistance profiles. Similarly, the diagnostic scope is variable, with some platforms targeting specific pathogens or panels of pathogens and others offering untargeted or broad-range evaluations.

Observational studies have not individually demonstrated an association between molecular testing strategies and improved clinical outcomes (52–65). Given the diversity of molecular tests used across studies, it was not possible to perform a valid meta-analysis. One RCT performed in neonates did find reduced mortality from 17.8% to 3.2% with therapy based on outcomes of a multiplex polymerase chain reaction-based molecular diagnostic system compared with reliance on traditional blood culture results (66). Data from RCTs in adults have not demonstrated a consistent reduction in mortality (67).

While the panel acknowledged potential benefits of rapidly identifying pathogens and resistance genes to expedite effective treatment, there remains considerable uncertainty about the application of molecular testing across settings with various epidemiological patterns of infection, potential for false-positive or misleading results, and concerns about the resources required for implementation of these novel diagnostic tests. Furthermore, the panel considered that implementation of laboratory-based adjunctive tests, such as Matrix-Assisted Laser Desorption/Ionization and Time-of-Flight mass spectrometry, for rapid species identification after traditional blood culture is likely beyond the decision scope of the treating clinician. Consequently, the panel issued no recommendation and emphasizes the importance of well-designed RCTs focused on both clinical outcomes and cost-effectiveness to better understand the impact of routine molecular testing for pathogen detection or identification in children with sepsis or septic shock.

B. ANTIMICROBIAL THERAPY

6. **For children with suspected septic shock, we recommend starting antimicrobial therapy as soon as possible, ideally within 1 hour of recognition of sepsis (strong recommendation, very low certainty of evidence).**

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7. **For children with probable sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for sepsis is substantiated, starting antimicrobial therapy as soon as possible after appropriate evaluation, ideally within 3 hours of recognition (conditional recommendation, very low certainty evidence).**
8. **For children with probable bacterial sepsis, where timely evaluation is difficult and there may be a delay due to other issues in clinical care, clinicians should consider giving antibiotics as soon as possible (GPS).**

Change From 2020 Guidelines: Updated recommendation.

Rationale: Compared with the prior 2020 guidelines, the panel issued no changes to the direction or certainty of evidence for these recommendations. There remains strong biological rationale to administer antimicrobials targeting the likely cause of sepsis (in particular, bacterial sepsis) as rapidly as possible. However, given overlap in symptoms of many children with sepsis and other clinical conditions, the urgency to administer empiric antimicrobial therapy must be balanced with the need for appropriate use and attention to concurrent or ongoing resuscitative therapies. In a retrospective study of 19,515 children who presented to emergency departments (EDs) across 51 U.S. hospitals, both early (< 30 min) and late (> 330 min) administration of antimicrobials were linked to mortality compared with more intermediate time intervals, especially in the subset with bacteremia (68). Overall, a meta-analysis of observational studies found that administration of antibiotics within 2 hours was associated with an OR (0.51; 95% CI, 0.22–1.19) for mortality (32, 35, 38, 68–70).

For children without shock, a time-limited period of rapid investigation and observation remains appropriate to allow substantiation of a presumptive diagnosis of sepsis and an opportunity to test for other causes of the patient's illness before giving antibiotics (71). However, in some healthcare settings (especially those with limited resources), when comprehensive diagnostic testing may not be feasible, a high likelihood of sepsis and severity of illness may still justify administering antibiotics as soon as possible. The panel also noted that because the 2024 Phoenix criteria for sepsis and septic shock sought to confirm those children with infection at high risk of mortality rather than identifying criteria for early recognition (19), initiating antimicrobial therapy before a child meets (or is known to meet) Phoenix criteria is often justified based on clinical assessment of a patient and projected course of illness.

For children with clinical evidence of septic shock, antimicrobial therapy should be initiated as soon as possible and ideally within 1 hour of recognition. For children with probable sepsis but without shock, antimicrobial therapy should be administered within 3 hours. For this later group, the panel emphasized the importance of an expedited diagnostic evaluation to determine causes, such as alternative diagnoses other than sepsis or likely viral pathogens, for which urgent antimicrobial therapy may not be needed. The panel also issued a new GPS to consider giving antibiotics as soon as possible if timely evaluation is difficult and there may be a delay due to other issues in clinical care, such as in healthcare systems with limited resources. Inherent within these recommendations is an awareness of the harms of antimicrobial overuse and resistance as an undesirable effect. Finally, the panel emphasized the need for further research to delineate optimal risk stratification and antibiotic de-escalation strategies.

9. **Clinicians should administer empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (GPS).**

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

10. **For children treated for sepsis or septic shock with immune compromise and/or are at high risk for multidrug-resistant pathogens, we suggest using empiric multidrug therapy (conditional recommendation, very low certainty of evidence).**

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

11. **For children with confirmed bacterial sepsis being treated with beta-lactam antibiotics, there was insufficient evidence to recommend for or against using a continuous and/or extended infusion strategy, compared with intermittent dosing.**

Change From 2020 Guidelines: New recommendation.

Rationale: The efficacy of beta-lactam antibiotics is dependent on the duration of free antibiotic concentration above the minimum inhibitory concentration for optimal antibacterial activity. For children with a confirmed bacterial etiology of sepsis, there was insufficient direct evidence that continuous and/or

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extended infusion strategies provide enhanced antibacterial activity or improve outcomes compared with intermittent dosing for those being treated with beta-lactam antibiotics (72). RCTs to date have not demonstrated a clear difference in mortality with continuous or extended infusions of beta-lactam antibiotics compared with standard intermittent dosing for children with sepsis or septic shock (RR, 0.58; 95% CI, 0.17–2.01) (73–78). In contrast, a meta-analysis of RCTs in adults with sepsis did demonstrate a small reduction in all-cause 90-day mortality for continuous infusion of beta-lactam antibiotics compared with standard intermittent dosing (RR, 0.91; 95% CI, 0.85–0.97) (74). Due to important pharmacokinetic differences across the spectrum of growth and development throughout childhood, as well as concerns with feasibility, safety, and drug stability and compatibility (72, 79–81), the indirect adult evidence was considered insufficient to warrant a recommendation. However, children in whom a bacterial pathogen susceptible to beta-lactam antibiotics has been confirmed may represent a target group who could benefit from continuous infusions (82). Further research is required to optimize antibiotic administration, including comparisons of continuous, extended, and intermittent delivery strategies, before recommendation of routine implementation in clinical practice (79).

12. Once the pathogen(s) and susceptibilities are available, empiric antimicrobial therapy coverage should be narrowed (GPS).

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

13. If no pathogen is identified, clinicians should narrow or stop empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice (GPS).

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

14. For children with sepsis or septic shock treated with antimicrobial therapy, we suggest not using procalcitonin routinely to guide de-escalation of therapy when effective antimicrobial stewardship programs are in place (conditional recommendation, moderate certainty of evidence).

Change From 2020 Guidelines: New recommendation.

Rationale: Timely de-escalation of antimicrobial therapy after infection has been excluded or eradicated can reduce patient harm related to unnecessarily prolonged antimicrobial treatment and reduce risks of antimicrobial resistance. For some infections (e.g., *Staphylococcus* bacteremia), a clear duration of antimicrobial therapy is available. However, even some recommended antimicrobial treatment durations are based on low quality of evidence, and the best strategy to safely discontinue antibiotics for presumed infections without a defined duration of therapy remains a particular challenge. The use of procalcitonin as a biomarker to guide antibiotic discontinuation decisions has been studied in one neonatal and one large multisite pediatric randomized trial. Across these two studies, there were no differences in mortality (RR, 0.52; 95% CI, 0.20–1.33) or duration of antibiotic use (MD, 3.85 hr fewer; 95% CI, 10.93 fewer to 3.24 greater hours) with a procalcitonin-guided strategy for antimicrobial de-escalation compared with usual care that included mature antimicrobial stewardship (83, 84). Although the panel acknowledged that procalcitonin has been found to safely reduce antibiotic duration in studies of adult patients with sepsis, given the availability of pediatric data without certainty of benefit along with moderate costs of incorporating procalcitonin into antimicrobial de-escalation decisions, the panel issued a conditional recommendation to not use procalcitonin routinely to guide de-escalation of therapy when effective antimicrobial stewardship programs are in place for pediatric sepsis and septic shock. The added value of a biomarker such as procalcitonin is likely dependent on the context and on the effectiveness of overall antimicrobial stewardship infrastructure and culture. Future research should focus on how best to implement antibiotic discontinuation in children with sepsis or septic shock and compare the role of procalcitonin (and other biomarkers) embedded in decision support systems.

15. For children with sepsis or septic shock with documented bloodstream infection, we suggest hospitals implement routine infectious diseases or medical microbiology consultation for management advice (conditional recommendation, very low certainty of evidence).

16. For children with sepsis or septic shock without documented bloodstream infection, there was insufficient evidence to provide a recommendation about whether hospitals should implement routine infectious diseases consultation.

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Change From 2020 Guidelines: New recommendation.

Rationale: Effective antimicrobial treatment requires expertise in choice, dose, route, and duration to optimize recovery from sepsis while limiting adverse effects. Specialists with expertise in the diagnosis and management of infectious diseases can enhance care for children with sepsis. Several observational studies have evaluated the effect of routine infectious diseases consultation on management and outcomes of children with bloodstream infections due to individual pathogens such as *Staphylococcus aureus*, *Candida* species, or *Enterococcus* species When pooled together, routine infectious diseases consultation for children with confirmed bloodstream infection is associated with improved mortality (RR, 0.51; 95% CI, 0.28–0.92) (85–90). Given practical resource, capacity, and equity implications, the importance of infectious diseases expertise was felt to be most relevant for patients with confirmed bloodstream infections in both high- and low-resource settings. While it is possible that some patients without a documented bloodstream infection would also benefit from consultation, there was insufficient evidence to issue a routine recommendation.

C. SOURCE CONTROL

17. **Emergent source control intervention should be implemented as soon as possible after a diagnosis of an infection amenable to a source control procedure (GPS).**

Remark: Appropriate diagnostic testing to identify the site of infection and microbial etiology should be performed, and advice from specialist teams (e.g., infectious diseases, surgery) should be sought, as appropriate, in order to prioritize interventions needed to achieve source control.

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

18. **For children with sepsis or septic shock, we recommend removal of intravascular access devices that are confirmed to be the source of sepsis or septic shock after other vascular access has been established and depending on the pathogen and the risks/benefits of a surgical procedure (strong recommendation, low certainty of evidence).**

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

D. FLUID THERAPY

19. **For children with septic shock being treated in healthcare systems with intensive care availability, we suggest administering up to 40–60 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour of initial resuscitation, over no fluid bolus (conditional recommendation, low certainty evidence).**
20. **For children with sepsis without hypotension being treated in healthcare systems with no intensive care availability, we recommend against using fluid bolus therapy, while starting maintenance fluids (strong recommendation, high certainty evidence).**
21. **For children with septic shock with hypotension being treated in healthcare systems with no intensive care availability, we suggest administering up to 40 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour of initial resuscitation over no fluid bolus therapy (conditional recommendation, low certainty evidence).**
22. **Hemodynamic status should be reassessed after every fluid bolus. Fluid bolus therapy should be titrated to clinical markers of cardiac output and discontinued if shock resolves or if signs of fluid overload develop (GPS).**

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

23. **For the initial resuscitation of children with sepsis or septic shock, we suggest using crystalloids, rather than albumin (conditional recommendation, moderate certainty of evidence).**

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

24. **For children with septic shock requiring treatment with fluid boluses, we suggest resuscitation with balanced or buffered crystalloid solutions over 0.9% saline (conditional recommendation, very low certainty of evidence).**

Remark: Balanced or buffered crystalloid solutions include, but may not be limited to, lactated Ringer's, Hartmann's solution, and other similar multiple electrolyte solutions. If balanced or buffered crystalloids are not readily available, fluid resuscitation with 0.9% saline is a suitable alternative. For some children with electrolyte abnormalities (e.g., hyponatremia) or concern for increased intracranial pressure (such as with CNS infections), the use of 0.9% saline may be preferred.

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Change From 2020 Guidelines: No change after review.

Rationale: The 2020 suggestion to use balanced/buffered crystalloids, rather than 0.9% saline, for the initial resuscitation of children with septic shock was based primarily on evidence from observational studies in children and indirect RCTs in adults that suggested resuscitation with crystalloid fluids containing high chloride concentrations (e.g., 0.9% saline) was associated with increased hyperchloremic acidemia, systemic inflammation, acute kidney injury (AKI), and mortality compared with resuscitation with balanced/buffered crystalloids (e.g., lactated Ringer's). More recently, five RCTs have compared clinical outcomes between critically ill children allocated to either balanced/buffered crystalloids to 0.9% saline, four of which focused exclusively on children with septic shock (91–94) and one included all children admitted to a PICU (95). All-cause mortality across these five RCTs was not different between the groups treated with balanced/buffered crystalloids or 0.9% saline (RR, 1.0; 95% CI, 0.82–1.22) (91–94). Similarly, among two RCTs with available data, there was no difference in all-cause mortality at 30 days (RR, 0.98; 95% CI, 0.80–1.21) (92, 94). AKI was also not different between groups (RR, 0.94; 95% CI, 0.53–1.66) (91–95), but the largest RCT conducted across four PICUs in tertiary care centers in India did demonstrate a lower incidence of new and/or progressive AKI among those children randomized to receive balanced/buffered crystalloid fluid boluses (73/351, 21%) compared with 0.9% saline (119/357, 33%) with a RR of 0.62 (95% CI, 0.49–0.80) (95). Among three RCTs, there was also a lower risk for needing renal replacement therapy (RRT) among those randomized to balanced/buffered crystalloids compared with 0.9% saline (RR, 0.58; 95% CI, 0.39–0.87) (91, 92, 94), although this difference was largely driven by one study (95). There were no differences in ventilator-free days, vasoactive-free days, or new-onset multiple organ dysfunction syndrome (MODS)-free days at day 28 between fluid types.

Although indirect evidence from adult RCTs was not considered for this recommendation, it is notable that a recent meta-analysis of six RCTs in critically ill adults with sepsis reported a RR for 90-day mortality of 0.93 (95% CI, 0.86–1.01) among balanced/buffered crystalloids compared with 0.9% saline (96). Finally, while 0.9% saline is generally less expensive than some balanced/buffered crystalloid options, the cost difference in most settings was judged to be low.

Therefore, based on the lower incidence of new and/or progressive AKI and RRT with balanced fluid in the largest pediatric RCT to date without a signal for harm across multiple RCTs and while pediatric data from further studies are pending, such as the ongoing the PRagMatic Pediatric Trial of Balanced vs. nOrmaL Saline FlUid in Sepsis (PRoMPT BOLUS) RCT with a planned sample size of 8800 children with septic shock (97), the panel issued a conditional recommendation that balanced/buffered crystalloids should generally be preferred over 0.9% saline for resuscitation of children with septic shock without a specific indication for an alternative fluid type (e.g., 0.9% saline may be preferred in patients with hyponatremia or concern for increased intracranial pressure) and when fluid compatibility concerns can be mitigated (e.g., second IV site or adequate flushing of a single IV site).

E. HEMODYNAMIC MONITORING

25. Resuscitation for children with sepsis or septic shock should be guided by ongoing clinical assessment of markers of hemodynamic status, including heart rate, blood pressure, capillary refill time, extremity temperature, pulse quality, level of consciousness, and urine output (GPS).

Change From 2020 Guidelines: New recommendation.

Rationale: Successful resuscitation from shock traditionally relies on global, repeated assessments of hemodynamic status that indicate improvement in markers of peripheral perfusion, such as heart rate, blood pressure, capillary refill time, extremity temperature, pulse quality, level of consciousness, and urine output. Although there are limited data about the use of these parameters either in isolation or combination to guide initial resuscitation in children and application at the bedside may be influenced by subjective assessment, such clinical assessment is accessible, inexpensive, and grounded in physiologic plausibility.

A recent study suggested that the 0-hour age-adjusted shock index (calculated by dividing heart rate by systolic blood pressure) performed better than conventional vital signs to predict need for vasoactive infusions or mechanical ventilation and early mortality, while the 6-hour score offered less utility (98). However, this observational study was deemed to

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have very low certainty results to recommend use of the shock index for routine hemodynamic monitoring. The ANDROMEDA-SHOCK trial in adult septic shock demonstrated that a resuscitation strategy targeting normalization of capillary refill time in the first 8 hours resulted in less organ dysfunction than targeting blood lactate decrease/normalization, although there was no difference in mortality (99). A perfusion-targeted approach still requires validation in pediatric clinical trials.

Therefore, for children with sepsis or septic shock, there was insufficient evidence to issue a GRADE recommendation to use clinical markers of altered perfusion to guide initial resuscitation. However, unless and until new data demonstrate utility and feasibility of an alternative monitoring strategy, the panel concluded that a GPS that initial resuscitation should be guided by ongoing clinical assessment of markers of hemodynamic status is warranted.

In our practice, initial resuscitation is guided by ongoing clinical assessment of several markers of hemodynamic status, including blood pressure (often used by 93% of the panel), heart rate (87%), capillary refill time (77%), level of consciousness (71%), urine output (69%), pulse quality (48%), and extremity temperature (41%).

26. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation about whether to target mean arterial blood pressure at the 5th or 50th percentile for age.

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

27. For children with septic shock, we suggest targeting central venous oxygen saturation ($Scvo_2$) greater than or equal to 70% when central venous access is available, over not targeting $Scvo_2$ (conditional recommendation, very low certainty evidence).

Remark: $Scvo_2$ is ideally measured from a central venous catheter (CVC) with the tip close to the right atrium.

Change From 2020 Guidelines: Updated recommendation.

Rationale: Until 2016, guidelines for adult septic shock recommended use of early goal-directed therapy (EGDT) based on a protocol published in 2001 (100). This approach targeted a series of "goals" that included $Scvo_2$. The rationale for targeting $Scvo_2$ greater than or equal to 70% is that lower values may reflect impaired oxygen delivery to tissues that could compromise oxygen consumption and create cellular stress. However, more recent studies of EGDT in adults failed to demonstrate a reduction in mortality compared with standardized treatment protocols that did not mandate $Scvo_2$ monitoring in three subsequent RCTs (101–103).

Two pediatric RCTs that included a combined 222 patients suggested a possible reduction in mortality with routine $Scvo_2$ monitoring (RR, 0.48; 95% CI, 0.22–1.03) (104, 105). The occurrence of new organ dysfunction was also in the direction of benefit, but the requirement for renal replacement therapy trended toward harm with wide CIs. Thus, the panel issued a conditional recommendation to target $Scvo_2$ greater than or equal to 70% when central venous access is available over not targeting $Scvo_2$. Notably, due to practical or financial constraints in some settings (e.g., ED, low-resource healthcare systems), this recommendation may not be universally applicable.

28. For children with sepsis and septic shock, there was insufficient evidence to issue a recommendation on use of advanced hemodynamic monitoring along with bedside clinical signs to guide resuscitation.

Change From 2020 Guidelines: Updated recommendation.

Rationale: Advanced hemodynamic monitoring devices measure parameters related to cardiac output, blood flow, and oxygen delivery and offer an adjunct to clinical markers of perfusion, such as blood pressure or $Scvo_2$ (106). In particular, cardiac output can be measured using several different approaches, although the most reliable methods require invasive catheters, such as central venous and/or arterial catheters) (106, 107). In theory, such monitoring offers an objective assessment of hemodynamic status to distinguish between low, normal, or high cardiac output states and to assist in evaluating the effect of hemodynamic interventions, such as fluid boluses or vasoactive medications. Unfortunately, high-quality studies demonstrating benefit for available monitors in pediatric septic shock are currently lacking and published recommendations are largely based on opinion rather than RCTs (108).

Echocardiography can also provide information about cardiac function and output though data are available only intermittently, results can vary based on the experience of the operator, and results may

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not be directly comparable to more invasive measurements (109, 110). Still, use of point-of-care ultrasound (POCUS) to assess cardiac function outside of formal echocardiography training is increasing and has shown utility (111). For example, in a single-centered retrospective observational study of 71 children with septic shock admitted to a PICU, incorporation of cardiac POCUS within 72 hours of sepsis pathway initiation changed a clinician's characterization of hemodynamic status in 67% of cases (112). In an RCT of 90 children admitted to a PICU in Egypt, addition of serial echocardiography provided early recognition of septic myocardial dysfunction and hypovolemia that was not apparent on clinical assessment and resulted in faster shock reversal, less fluid overload, shorter LOS, and lower mortality compared with the group without serial echocardiography (111). Notably, both echocardiography and some advanced hemodynamic monitoring methods can, under certain conditions, help to predict whether a fluid bolus will increase stroke volume or cardiac output (e.g., fluid responsiveness) by estimating peak flow variations in the aorta (113). While this can be of clinical importance, even reliable prediction of fluid responsiveness itself does not necessarily imply that the patient will benefit overall.

In our practice, 71% of the panel use some form of advanced hemodynamic monitoring along with bedside clinical signs to guide resuscitation in children with sepsis and septic shock. The most used modalities were echocardiography or cardiac POCUS (32%), pulse index continuous cardiac output (32%), or suprasternal/transthoracic aortic Doppler ultrasound (22%).

29. For children with sepsis or septic shock, we suggest using cardiac and lung POCUS to guide resuscitation, over not using POCUS to guide resuscitation, if local training and resources allow (conditional recommendation, low certainty evidence).

Change From 2020 Guidelines: New recommendation.

Rationale: POCUS is the acquisition, interpretation, and immediate clinical integration of ultrasonographic imaging performed by a treating clinician at the patient's bedside. POCUS has become widespread in its availability and use in pediatric acute care in both resource-rich and limited settings. For children with sepsis or septic shock, POCUS has the potential to assist in assessing for myocardial dysfunction, pulmonary hypertension, and potential fluid responsiveness. POCUS can assist to identify both signs of hypovolemia leading to low preload and signs of fluid overload such as pulmonary edema and pericardial/pleural effusions. POCUS has been proven effective to identify reversible causes of shock and differentiate hypovolemia, cardiogenic, and obstructive etiologies, which can all be present during and/or mimic septic shock (114). Clinical evidence supports the utility of POCUS to assess both heart and lung function. For example, in a study of 46 children with suspected septic shock, cardiac POCUS performed within 72 hours of sepsis recognition changed the characterization of patients' hemodynamic status in 67% of cases (112). Lung POCUS has demonstrated correlation with other parameters of lung mechanics and gas exchange (112, 115, 116).

The impact of cardiac and lung POCUS-guided management on patient outcomes, however, remains limited. A meta-analysis of two small pediatric single-center RCTs demonstrated that POCUS-guided management was associated with shorter shock reversal time (MD, 24 hr lower; 95% CI, 10.8–37.1 hr lower) and shorter PICU LOS (MD, 3.6 d lower; 95% CI, 1.4–5.9 d lower) (111, 117). In one study, cumulative fluid balance was lower in the POCUS-guided management group, but this association was not evident in the pooled analysis.

Given that POCUS is an accessible diagnostic modality, even in many resource-limited settings, that has the potential to augment clinical assessment of heart and lung function with some evidence of benefit to patient outcomes, the panel issued a conditional recommendation to use cardiac and lung POCUS to guide resuscitation if local training and resources allow. Future research is needed to evaluate the full clinical impact of POCUS-guided sepsis resuscitation on patient outcomes across healthcare settings and to optimize POCUS-guided sepsis management of fluid, vasoactive, and ventilation therapies.

F. VASOACTIVE MEDICATIONS

30. For children with septic shock, there was insufficient evidence to issue a recommendation on initiating vasoactive medications either before or after 40 mL/kg of bolus fluid therapy.

Change From 2020 Guidelines: New recommendation.

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Rationale: The prior 2020 guidelines included a remark that it is reasonable to begin vasoactive infusions after 40–60 mL/kg of fluid resuscitation if the patient continues to have evidence of shock, or sooner if fluid overload develops or other concerns for fluid administration are present. Available data at that time were largely from observational studies that demonstrated improved outcomes in children with septic shock treated with up to 60 mL/kg of fluid resuscitation within the first hour of presentation (32, 118–127).

Data are now available from three small RCTs comparing vasoactive medication initiation after either no more than 40 mL/kg or after 40–60 mL/kg fluid bolus therapy (121, 128, 129). Pooled data from these studies did not identify differences in mortality (RR, 0.62; 95% CI, 0.23–1.69), proportion with or time to resolution of shock, or other clinical outcomes between groups. In general, patients randomized to receive earlier vasoactive medications received less overall fluid administration. For example, in a multicenter pilot study of 40 children with septic shock, the median time from randomization to epinephrine initiation was 16 minutes (interquartile range [IQR], 12–26 min) in the intervention group that started vasoactive medications after only 20 mL/kg compared with 49 minutes (IQR, 29–63 min) in the standard care group that received an initial 40–60 mL/kg. In this study, the median amount of fluid delivered during the first 24 hours was 0 mL/kg (IQR, 0–10 mL/kg) in the intervention group and 20 mL/kg (IQR, 14.6–28.6 mL/kg) in the standard group (difference, –20.0; 95% CI, –28.0 to –12.0) (128). Notably, differences in study design, setting, and population made it challenging to fully interpret the data in aggregate.

Data were limited about the resources required to initiate early vs. later vasoactive medications or the cost-effectiveness of treating with early vasoactive medications compared with additional fluid administration. However, while the healthcare setting may influence the choice of when to commence vasoactive medications in practice, the panel noted that both fluid bolus therapy and vasoactive medications are readily available across both high- and low-resource settings.

Given the absence of a clear benefit on the timing of vasoactive medications relative to the volume of fluid bolus therapy, the panel acknowledged that there was insufficient evidence to issue a recommendation and that it is reasonable to initiate vasoactive medications either before or after 40 mL/kg of bolus fluid therapy. Further data are expected soon from the SQUEEZE trial comparing immediate initiation of vasoactive medications to fluid bolus therapy up to 60 mL/kg followed by initiation of vasoactive medications in children with septic shock (130).

In our practice, 63% of the panel often or sometimes initiate vasoactive medications before 40 mL/kg of bolus fluid therapy, noting that decisions to initiate early vasoactive medications before 40 mL/kg are most influenced by the presence of severe hypotension, altered mental status, delayed capillary refill, mottled skin, cyanosis, and ashen appearance.

31. For children with septic shock requiring vasoactive medications, there was insufficient evidence to issue a recommendation on the preferred use of epinephrine or norepinephrine for first-line therapy in children with septic shock.

Change From 2020 Guidelines: Updated recommendation.

Rationale: Epinephrine and norepinephrine are both widely used in pediatric septic shock, and both have vasoconstrictor and inotropic properties. In the 2020 iteration, we were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock due to a lack of relevant trials directly comparing epinephrine with norepinephrine. More recently, an RCT of 67 children comparing first-line treatment with epinephrine to norepinephrine plus dobutamine was completed (131). In this trial, there were no differences in shock resolution at 1 hour (RR, 2.0; 95% CI, 0.54–7.35), hospital LOS, or 28-day mortality, although children in the norepinephrine plus dobutamine group attained shock resolution slightly earlier (HR, 1.84; 95% CI, 1.1–3.08). An important limitation of this study was the high degree of crossover and use of other vasoactive agents (82% in the epinephrine group and 30% in the norepinephrine group). In a propensity-matched analysis of 231 pediatric sepsis episodes without evidence for myocardial dysfunction, there was no difference in the primary outcome of major adverse kidney events by 30 days between first-line treatment with epinephrine or norepinephrine (6.1% vs. 4.1%) but epinephrine was associated with greater 30-day mortality compared with norepinephrine (3.7% vs. 0%; risk difference, 3.7%; 95% CI, 0.2–7.2%) (132). However, despite use of propensity score matching, the groups differed in important

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ways, including timing and location (ED vs. PICU) of vasoactive medication initiation, that made it difficult to remove the impact of confounding influences.

Overall, evidence remained insufficient to recommend either epinephrine or norepinephrine as a first-line vasoactive strategy in children in septic shock. There continued to be a general preference for epinephrine to treat myocardial dysfunction and low cardiac output, and norepinephrine to increase systemic vascular resistance. Until further data are available, the panel determined that it is reasonable to use either epinephrine or norepinephrine based on individual patient physiology, local system factors, and clinician preference. Further research comparing epinephrine with norepinephrine for first-line therapy in children with septic shock is needed.

In our practice, 57% of the panel more commonly uses epinephrine as first-line therapy and 43% more commonly use norepinephrine.

32. For children with septic shock requiring vasoactive medications, we suggest initiating vasoactive medications through peripheral venous access over delaying therapy until central venous access is obtained (conditional recommendation, very low certainty of evidence).

Change From 2020 Guidelines: Updated recommendation.
Rationale: In the 2020 guideline, we were unable to issue a recommendation about initiation of vasoactive agents through peripheral access in children with septic shock but noted that the panelists often or sometimes administered a dilute concentration of vasoactive medication (including epinephrine, norepinephrine, or dopamine) through a peripheral vein if central venous access was not readily accessible. We also suggested that central venous access should be obtained as soon as reasonably practicable. These statements were mainly based on a survey of panelists and one retrospective observational study (133).

Across six new observational studies with a total of 709 children (133–138), a meta-analysis showed a reduced risk of death with initial administration of vasoactive medications through peripheral venous access (RR, 0.45; 95% CI, 0.3–0.67). There was a low risk of extravasation injury with peripheral venous access of 2.5% (95% CI, 1.69–4.2%). Extravasation events tended to be associated with peripheral access in a distal extremity, particularly the hand. Unfortunately, data were not reported about time to shock resolution, which might be a potential benefit of earlier initiation of vasoactive agents through peripheral venous access. Although data were also not available about costs and savings, there is unlikely to be much difference between peripheral or central venous administration of vasoactive medications. Although CVCs do cost more than peripheral catheters, it is anticipated that many patients in whom vasoactive drugs are commenced peripherally will eventually have a CVC placed. The use of peripheral access before insertion of a CVC is expected to facilitate more timely delivery of vasoactive drugs in all settings, particularly the pre-PICU environment, and in settings with limited resources (139–141).

33. For children with septic shock who require high-dose catecholamines, we suggest either adding vasopressin or further titrating catecholamines (conditional recommendation, low certainty of evidence).

Change From 2020 Guidelines: No change, carried over.
Rationale: See 2020 Guidelines for rationale.

34. For children with septic shock and cardiac dysfunction despite treatment with initial vasoactive medications, there was insufficient evidence to issue a recommendation about adding an inodilator.

Change From 2020 Guidelines: No change, carried over.
Rationale: See 2020 Guidelines for rationale.

35. For children with septic shock with persistent hypoperfusion despite treatment with other vasoactive medication, there was insufficient evidence to issue a recommendation for co-treatment with angiotensin II.

Change From 2020 Guidelines: New recommendation.
Rationale: Persistent septic shock despite fluid resuscitation and use of vasoactive medications is associated with high mortality. Angiotensin II is a naturally occurring hormone with vasoconstrictor effects that has the potential to increase the low systemic vascular resistance contributing to septic shock with persistent hypoperfusion in some patients. Potential mechanisms by which angiotensin II may counteract shock include vasoconstriction, water and sodium retention, and potentiation of catecholamine activity. In the 2021 SCCM guideline on management of adult sepsis (67), angiotensin II was considered for use as an adjunctive vasopressor medication based on two RCTs of adult patients. One small study of 20 patients demonstrated physiologic efficacy without safety concerns (142) and

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a second, larger RCT of 344 patients in patients with vasodilatory shock (most of whom had confirmed or presumed sepsis) (143) that showed increased mean arterial pressure in the angiotensin II group; however, mortality did not differ between those allocated to angiotensin II or titration of norepinephrine. Both of these studies were considered to be too indirect to inform a pediatric recommendation.

Three studies were identified on the use of angiotensin II for pediatric septic shock, but all were small retrospective case series or case reports (144, 145), and considered to not to be of sufficient quality to inform a recommendation. Therefore, the panel could not issue a recommendation about the use of angiotensin II for persistent vasodilatory septic shock in children.

In our practice, 8% of the panel sometimes use angiotensin II for children with septic shock with persistent hypoperfusion despite treatment with other vasoactive medications, while 10% rarely and 82% almost never use angiotensin II in this setting.

36. For children with septic shock with persistent hypoperfusion despite treatment with other vasoactive medications, there was insufficient evidence to issue a recommendation for co-treatment with methylene blue.

Change From 2020 Guidelines: New recommendation.

Rationale: The nitric oxide (NO) pathway likely contributes to hypotension in septic shock, although the exact mechanism is not fully understood. Increased production of NO through up-regulation of inducible NO synthase (NOS) may stimulate vasodilation outside of usual vasoregulatory mechanisms, while NOS inhibitors may be detrimental to microcirculation and immune function. Methylene blue specifically inhibits soluble guanylate cyclase within the NO pathway and is hypothesized to counteract hypotension without impacting some of the positive effects of NO.

One single-center RCT compared methylene blue to terlipressin as adjunct therapies to conventional management in 30 infants treated for refractory septic shock in a neonatal ICU in Egypt (146). This study demonstrated a more rapid improvement in blood pressure in the group treated with methylene blue group but blood pressure overall improved in both groups and there was no difference in mortality (66% vs. 60%). The totality of indirect adult and limited pediatric data did not provide sufficient evidence for the panel to issue a recommendation for co-treatment with methylene blue for children with persistent vasodilatory septic shock.

In our practice, only 8% of the panel often or sometimes use methylene blue for children with septic shock with persistent hypoperfusion despite treatment with other vasoactive medications, while 62% rarely or almost never use methylene blue in this setting.

G. VENTILATION

The panel deferred to guidelines on pediatric ARDS for management of noninvasive and invasive mechanical ventilation and adjunctive therapies in children with sepsis or septic shock that are not otherwise addressed in these guidelines (13, 147).

37. For children with fluid-refractory, catecholamine-resistant septic shock, there was insufficient evidence to issue a recommendation about whether to intubate in the absence of respiratory failure.

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

38. For children with sepsis or septic shock, we suggest against using etomidate when intubating (conditional recommendation, low certainty of evidence).

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

39. For children with sepsis or septic shock following resuscitation, we suggest titrating supplemental oxygen to target a conservative range (peripheral oxygen saturation [Spo_2] 88–92%) over a more liberal target (Spo_2 > 94%; conditional recommendation, moderate certainty of evidence).

Change From 2020 Guidelines: New recommendation.

Rationale: Supplemental oxygen is used to prevent and treat hypoxia in children with sepsis but the harms of hyperoxia, through free-radical damage and microcirculatory changes, may also be detrimental (148–151). Limiting oxygen use by defining optimal Spo_2 targets may improve clinical outcomes and reduce inequities in care in contexts where access to therapeutic oxygen is limited (152).

We identified four RCTs evaluating liberal vs. lower Spo_2-targeted strategies in children (153–156).

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These trials included, but were not restricted to, children with sepsis. Three studies used Spo_2 greater than 94% as a threshold of liberal oxygenation and either Spo_2 88–92% or 90–94% as the conservative target. The fourth study, conducted in resource-restricted settings, compared high-flow, low-flow, or no oxygen in children with Spo_2 values between 80% and 91%, titrating supplemental oxygen to maintain an Spo_2 less than 92%. The pooled estimates demonstrated shorter length of hospital stay (RR, 0.39; 95% CI, 0.11–0.66), reduced duration of mechanical ventilation, and fewer adverse effects when oxygen was titrated to maintain lower Spo_2 targets. One trial also found that quality-adjusted life years were not different between groups but there was an overall incremental net monetary benefit at 1 year with conservative oxygenation (Spo_2 88–92%) in mechanically ventilated patients (157).

Notably, current World Health Organization guidance recommends oxygen therapy if Spo_2 is less than 90% or less than 94% if there are signs of shock or encephalopathy (158). However, among mechanically ventilated children, targeting an Spo_2 of 88–92% led to more days alive without organ support at day 30 compared with an Spo_2 target greater than 94% (153). While this Spo_2 range is lower than the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) recommendation to maintain Spo_2 92–97% for pediatric ARDS (which commonly accompanies sepsis), the PALICC-2 recommendations predated the OxyPICU trial (153).

Overall, the potential benefits of reducing time of mechanical ventilation and organ support without a signal for harm led the panel to issue a conditional recommendation to target a conservative range (Spo_2 88–92%) over a more liberal target (Spo_2 > 94%) for children after initial resuscitation. Although one RCT did not show differences in outcomes between the no oxygen and oxygen arms for patients in the Spo_2 80–91% range in resource-limited settings, the panel did not view that these Spo_2 targets were generalizable to children with sepsis/septic shock in all settings.

Despite a moderate certainty of evidence, the panel issued only a conditional recommendation for the following reasons. First, it is not clear if this recommendation should apply to children during the acute phase of resuscitation, as the risk-benefit balance of oxygenation may change during resuscitation for sepsis or septic shock. Second, children with severe anemia, hemoglobinopathies, cyanotic heart disease, markers of tissue oxygen debt, low cardiac output, and MODS that includes neurologic dysfunction may have different optimal Spo_2 targets. Third, Spo_2 monitors may be biased toward higher readings in those with darker skin tones (159, 160), although there was no indication that the benefits of conservative oxygenation differed in darker-skinned children (161). These uncertainties require further research that take into account the setting, availability of continuous Spo_2 monitoring, and the timing and level of the intervention.

H. CORTICOSTEROIDS

40. For children with septic shock in whom hemodynamic stability can be restored with fluid resuscitation and vasoactive therapy, we suggest against the use of IV hydrocortisone (conditional recommendation, low certainty of evidence).

Change From 2020 Guidelines: No change after review.

41. For children with septic shock who remain hemodynamically unstable despite adequate fluid resuscitation and vasoactive therapy, there was insufficient evidence to issue a recommendation on whether to treat with IV hydrocortisone.

Remark: Although routine use of corticosteroids in children with sepsis or septic shock is not recommended, stress-dose corticosteroids should be administered for suspected or documented adrenal insufficiency.

Change From 2020 Guidelines: Updated recommendation.

Rationale: The conditional recommendation to not use hydrocortisone for children with septic shock in whom hemodynamic stability can be restored with fluid resuscitation and vasoactive therapy alone remains unchanged from the prior 2020 guidelines, while the statement for children who remain hemodynamically unstable despite adequate fluid resuscitation and vasoactive therapy was updated to clarify that there was insufficient evidence to issue a recommendation. Since the 2020 guidelines, there is conflicting new evidence about the efficacy and safety of hydrocortisone use as adjunctive therapy in children with persistent septic shock with most observational pediatric studies suggesting potential harm. However,

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a recent meta-analysis that included 45 RCTs and 9563 adult and pediatric patients found that corticosteroids probably reduce short-term mortality (RR, 0.93; 95% CI, 0.88–0.99; moderate certainty) and increase shock reversal at 7 days (RR, 1.24; 95% CI, 1.11–1.38; high certainty) (162). Importantly, this study found no difference in mortality in children with use of corticosteroids and concluded that there was insufficient evidence to analyze other outcomes in children.

Several pediatric observational studies found that administration of corticosteroids was associated with increased mortality (163–165), while a meta-analysis of the six most recent observational studies (163–168) showed no differences in mortality (RR, 1.55; 95% CI, 0.65–3.7), RRT (RR, 3.38; 95% CI, 0.14–79.0), or extracorporeal membrane oxygenation (ECMO: RR, 3.38; 95% CI, 0.14–79.0). There were also no differences in the duration of vasopressor use (MD, 0.15; 95% CI, –0.78 to 1.08 d), vasopressor-free days (MD, 2.67; 95% CI, –7.46 to 12.08 d), or duration of mechanical ventilation (MD, –0.06; 95% CI, –3.81 to 3.69 d). However, the group receiving corticosteroids had fewer ventilator-free days (MD, –7.00; 95% CI, –13.65 to –0.35 d) and longer LOS in both the PICU (RR, 5.33; 95% CI, 1.84–8.81 d) and hospital (RR, 8.35; 95% CI, 3.08–13.62 d). In addition, one study found that duration of MODS was longer in patients with immune paralysis if corticosteroids were administered (164), whereas another study reported a 42% reduction in prolonged PICU stay greater than 6 days among patients receiving corticosteroids. Notably, the effect of corticosteroids does not seem to be modified by random serum total cortisol levels (165).

One study attempted to address heterogeneity of treatment effect by analyzing outcomes according to the Pediatric Sepsis Biomarker Risk Model (PERSEVERE)-II score. This study included 461 children with septic shock and reported that corticosteroid administration was associated with increased mortality and worse outcomes (e.g., complicated course, more failed organs, fewer ICU-free days) in children with a high PERSEVERE-II score (167).

Current pediatric studies remain limited by small sample sizes and retrospective study designs that, despite various statistical attempts, make it difficult to disentangle the effect of corticosteroids from confounding influences of illness severity. However, taken together, existing data with a signal of possible harm were sufficient to recommend against the routine use of corticosteroids in children with septic shock in whom hemodynamic stability can be restored with fluid resuscitation and vasoactive therapy in the absence of suspected or documented adrenal insufficiency. For children with sepsis with known or suspected adrenal insufficiency, stress-dose corticosteroids should be administered regardless of hemodynamic status. For children with septic shock who remain hemodynamically unstable despite adequate fluid resuscitation and vasoactive therapy, there was insufficient evidence to issue a recommendation on the use of hydrocortisone and, thus, it is reasonable to either use or not use IV hydrocortisone until further data from ongoing RCTs are available.

I. ENDOCRINE AND METABOLIC

The panel deferred to guidelines on glycemic control for management of blood glucose levels and use of insulin in children with sepsis or septic shock (169).

42. For children with sepsis or septic shock with fever, there was insufficient evidence to issue a recommendation on whether to target normothermia or take a permissive approach to fever.

Change From 2020 Guidelines: Updated recommendation.

Rationale: Compared with the prior 2020 guidelines that included a weak recommendation to either use antipyretic therapy or pursue a more permissive approach to fever, the new statement was updated to clarify that there was insufficient evidence to issue a recommendation on whether to target normothermia or take a more permissive approach to fever in children with sepsis or septic shock. Fever is an evolutionarily conserved immune process with survival benefits mediated by inhibiting growth of pathogens and potentiating the cellular immune response (170). However, whether these process are beneficial or represent a redundant energy inefficient process in children with sepsis is not known (171). Certainly, fever contributes to a child's (and likely parent's) feeling and perception of being unwell.

We identified a single pilot RCT for children admitted to the PICU that compared a restrictive approach to treat fever greater than or equal to 37.5°C to a more permissive approach treating fever only when greater than or equal to 39.5°C (172). There was a significant, albeit small, separation in mean body temperature

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between the arms of 0.5°C (95% CI, 0.2–0.8), but no differences in mortality, duration of ventilation, need for cardiovascular or kidney support, or PICU LOS. Notably, this feasibility study was not powered to test for difference in patient outcomes and the modalities to manage temperature were not specified. Additionally, because medications such as paracetamol/acetaminophen are commonly used for both antipyresis and analgesia in PICU patients, the extent of therapeutic crossover between study arms was not clear (173). Based on absence of evidence supporting a benefit for aggressive antipyretic therapies, we were not able to issue a recommendation on whether to target normothermia or take a more permissive approach to fever. The panel was also unable to comment on the impact of either strategy in resource-limited settings. While the cost of antipyretic interventions was viewed as low, potential indirect costs, such as prolonged hospitalization for observation with a permissive strategy, may need to be considered.

In our practice, 25% of the panel always and 44% often treat fever in patients with sepsis and septic shock to optimize patient comfort, reduce metabolic demand, and reduce extreme body temperatures. Only 7% of panelists almost never treat fever in sepsis or septic shock.

43. For children with sepsis or septic shock and metabolic acidemia, there was insufficient evidence to issue a recommendation on the use of sodium bicarbonate.

Change From 2020 Guidelines: New recommendation.
Rationale: Metabolic acidemia is common in patients with sepsis and septic shock (174) and use of sodium bicarbonate to counter such acidemia is commonly, but inconsistently employed (174, 175). Among critically ill adults, resolution of acidemia is associated with improved survival (175), yet specific administration of sodium bicarbonate for this purpose has not been demonstrated to improve survival. One notable group who might benefit from sodium bicarbonate administration is based on indirect evidence from critically ill adults with moderate-severe AKI with severe acidemia (pH ≤ 7.20, $Paco_2$ ≤ 45 mm Hg, and serum bicarbonate concentration ≤ 20 mmol/L) and MODS (176).

In pediatrics, two large retrospective studies (177, 178) examined the efficacy of sodium bicarbonate for metabolic acidemia among a combined 7460 critically ill children (overlap in patient cohorts between studies cannot be excluded). Patients with sepsis, pneumonia, and/or encephalitis accounted for 13.6% patients (798/5865) in one study, while patients with infection or sepsis were not specifically identified in the second study. After attempts to control for confounding using propensity score matching and multivariable regression, treatment with sodium bicarbonate was not associated with mortality, LOS, or time to resolution of organ dysfunction. A subsequent subanalysis demonstrated that sodium bicarbonate was associated with decreased mortality (adjusted OR, 0.52; 95% CI, 0.34–0.79) among patients with hyperchloremia (serum chloride > 113 mmol/L) and low anion gap less than 6, but mortality was increased among patients with lower serum chloride (< 107 mmol/L) and/or high anion gap greater than 12 (adjusted OR, 2.07; 95% CI, 1.44–2.97).

Overall, our review indicated trivial desirable effects, few undesirable effects, low cost and high accessibility (a potential advantage in low-resource settings), and very low certainty of evidence. The balance of these effects from available literature did not favor either the intervention or the comparison and, thus, the panel was not able to recommend for or against sodium bicarbonate administration in children with sepsis or septic shock with acidemia. The panel continued to support RCTs to address this knowledge gap.

In our practice, 7% of the panel always and 38% sometimes use sodium bicarbonate for children with sepsis or septic shock and metabolic acidemia, while 37% rarely and 18% almost never use sodium bicarbonate for metabolic acidemia during sepsis/septic shock. The most common clinical situations in which the panel considered use of sodium bicarbonate include severe metabolic acidemia with pH less than or equal to 7.10, AKI, and/or hyperchloremia greater than or equal to 110 mEq/L with concurrent ongoing hemodynamic instability and shock.

44. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation about whether to target normal blood calcium levels or tolerate hypocalcemia.

Change From 2020 Guidelines: No change, carried over.
Rationale: See 2020 Guidelines for rationale.

45. For children with sepsis or septic shock in a sick euthyroid state, we suggest against the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction (conditional recommendation, low certainty of evidence).

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Change From 2020 Guidelines: No change, carried over.
Rationale: See 2020 Guidelines for rationale.

J. NUTRITION

The panel deferred to guidelines on nutritional support for management of enteral and parenteral nutrition support in children with sepsis or septic shock (12, 16).

46. For children with sepsis or septic shock, we suggest against the use of vitamin C (ascorbic acid; conditional recommendation, very low certainty evidence).

Change From 2020 Guidelines: No change after review.

47. For children with sepsis or septic shock, we suggest against the use of thiamine (vitamin B1; conditional recommendation, very low certainty evidence).

Remark: The routine use of vitamin C or thiamine in children with sepsis or septic shock is not recommended. However, in the context of suspected or documented deficiency (e.g., malnutrition) both vitamin C or thiamine may be beneficial.
Change From 2020 Guidelines: No change after review.
Rationale: Vitamin C (ascorbic acid) and thiamine (vitamin B1) have been evaluated as adjunctive therapies in many studies of adult septic shock, often in combination with hydrocortisone, but pediatric data are limited (179–182). The rationale for use includes the antioxidant and anti-inflammatory effects of ascorbic acid and the role of thiamine in mitochondrial function and lactate metabolism (183, 184). In critically ill children with sepsis, low blood levels of vitamin C and thiamine are associated with illness severity, including risk of MODS and mortality (185, 186), and treatment with thiamine has been associated with improvement in physiologic and clinical outcomes after prolonged hyperlactatemia (187). However, high-quality evidence linking treatment with vitamin C and/or thiamine to clinical benefits in children with sepsis/septic is currently lacking.

The panel considered two pediatric RCTs on these topics. The RESPOND PICU trial was a multicenter, open-label RCT that randomized 60 children with septic shock to either vitamin C (30 mg/kg IV every 6 hr), thiamine (4 mg/kg IV every 12 hr), and hydrocortisone (1 mg/kg IV every 6 hr) or usual care for up to 7 days (188). In this pilot study not specifically powered to assess effects on clinical outcomes, there were no differences in days alive and free of organ dysfunction, PICU LOS, or shock reversal (median, 35.2; IQR, 14.6–101.2 hr in the intervention group vs. 47.3; IQR, 22.4–106.8 hr in the standard care group [MD, −12 hr; 95% CI, −56.8 to 32.7 hr]). The VITACiPS RCT randomized 218 children to either vitamin C (25 mg/kg IV every 6 hr) or placebo for 72 hours (189). There were no differences in the primary outcome of change in pediatric Sequential Organ Failure Assessment score from baseline to 72 hours between groups (MD, −0.51; 95% CI, −1.76 to 0.75) or 28-day mortality, shock reversal, or adverse events.

The panel considered the balance of effects, resource use, and feasibility to conclude that routine administration of vitamin C or thiamine in pediatric septic shock cannot be recommended. Although thiamine could potentially be beneficial with sustained hyperlactatemia, there are no high-quality pediatric data to confirm this possibility (187). The panel also considered a potential role for vitamin C and/or thiamine in patients at risk for deficiency (e.g., malnutrition, chronic illness), but current data do not justify general recommendations for routine use in all children with sepsis or septic shock. These recommendations align with adult guidelines that similarly caution against the routine use of vitamin C and/or thiamine for sepsis/septic shock outside the context of a clinical trial (67). Thus, until data from larger, adequately powered RCTs are available, clinicians should not routinely use vitamin C or thiamine for children with sepsis or septic shock. Consideration of vitamin C and/or thiamine repletion in select patients with malnutrition, suspected or documented vitamin deficiencies, and clinical symptoms attributable to these deficiencies remains reasonable.

48. For children with sepsis or septic shock, we suggest against the acute repletion of vitamin D in the absence of clinical vitamin D insufficiency (conditional recommendation, very low certainty of evidence).

Change From 2020 Guidelines: No change, carried over.
Rationale: See 2020 Guidelines for rationale.

K. BLOOD PRODUCTS

The panel deferred to guidelines on RBC, platelet, and plasma transfusion for the management of blood product utilization in children with sepsis or septic shock (14, 190).

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L. FLUID BALANCE, RENAL REPLACEMENT, AND EXTRACORPOREAL SUPPORT

49. It is reasonable to consider measures to prevent excessive fluid administration, monitor total fluid intake, and consider active fluid removal in case of fluid overload after hemodynamic stability is achieved and while closely monitoring hemodynamic changes to avoid compromising end-organ perfusion (GPS).

Change From 2020 Guidelines: New recommendation.
Rationale: For children with sepsis or septic shock, there was insufficient evidence available to issue a GRADE-based recommendation on the utility of an active approach to manage fluid overload after initial resuscitation. While observational studies have demonstrated that fluid overload is associated with adverse outcomes, including mortality, longer duration of mechanical ventilation, longer hospitalization, and lower health-reality quality of life (191–194), it is challenging to ascertain a causal effect due to the confounding effects of illness severity that serves as a major driver for fluid overload. There are no interventional pediatric studies examining the impact of active fluid management after initial sepsis resuscitation on outcomes. Thus, based on the consistency of harm observed with increasing fluid overload in observational studies, the panel issued a GPS that it is reasonable to consider measures to prevent excessive fluid administration, monitor total fluid intake, and consider active fluid removal in case of fluid overload after hemodynamic stability is achieved and while closely monitoring hemodynamic changes to avoid compromising end-organ perfusion.

In our practice, 64% of the panel target a negative fluid balance once hemodynamic stability has been achieved as evidenced by weaning of vasoactive medications and improved measures of organ perfusion/function and 31% target a negative fluid balance as soon as organ perfusion and function is improved irrespective of the level of vasoactive medication support. As a mode of active fluid removal after first using diuretic therapy, 58% of panel members consider either continuous renal replacement therapy (CRRT) or ultrafiltration to achieve negative fluid balance.

50. For children with sepsis or septic shock requiring renal replacement therapy, we suggest using high-volume hemofiltration (HVHF; > 35 mL/kg/hr) over standard-volume hemofiltration (≤ 35 mL/kg/hr; conditional recommendation, low certainty of evidence).

Change From 2020 Guidelines: Updated recommendation.
Rationale: CRRT can help to optimize acid-base and volume status in patients with hemodynamic instability and potentially mitigate the immunoinflammatory milieu compared with intermittent dialysis in critically ill patients. Use of HVHF during CRRT improves convection and adsorption for increased efficiency of removal of medium to larger size solutes, potentially enhancing clearance of pro- and anti-inflammatory mediators (e.g., cytokines) and toxins. HVHF uses a higher effluent rate, typically greater than 35 mL/kg/hr, than standard-volume hemofiltration, although does not yet have a standard universally accepted definition.

In the 2020 guidelines, the panel suggested against use of HVHF over standard-volume hemofiltration due to lack of evidence of benefit and a possible signal for increased hyperglycemia with HVHF in a single observational pediatric study (195). More recently, meta-analysis of three RCTs that included a total of 195 children with sepsis demonstrated lower mortality with HVHF compared with standard-volume hemofiltration (RR, 0.58; 95% CI, 0.34–0.98). Duration of RRT (MD, 1.2 d lower; 95% CI, –1.84 to –0.56) also favored HVHF vs. standard-volume hemofiltration, but PICU LOS was not different between groups (196–198). In two of these studies, serum cytokine levels were lower after treatment with HVHF compared with the standard-volume hemofiltration (197, 198).

Notably, the definition and timing of HVHF varied across these studies. One study focused on children with sepsis and AKI (197), while the other two included all children with sepsis. Additionally, the total combined sample size and event rates were relatively small, leading to the potential for type 1 error in the pooled analyses. Finally, all three trials used continuous venovenous hemofiltration (CVVH) as the modality of HVHF; thus, it remains unknown whether these findings may be extrapolated to other modalities such as continuous venovenous hemodialysis and continuous venovenous hemodiafiltration. While broader study across CRRT modalities in larger populations is warranted, the panel was able to issue a conditional recommendation to use HVHF (> 35 mL/kg/hr) over standard-volume hemofiltration (≤ 35 mL/kg/hr) based on the balance of positive effects of HVHF across the included trials. This recommendation is applicable

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to areas that have available resources for CRRT and HVHF acknowledging that this intervention may be either more expensive or not available in all settings.

51. For children with sepsis or septic shock who meet criteria for the thrombocytopenia-associated multiple organ failure (TAMOF) subphenotype, there was insufficient evidence to issue a recommendation on whether to treat with plasma exchange (PLEX).

Change From 2020 Guidelines: No change after review.

Rationale: The prior 2020 suggestion against use of PLEX in children with sepsis-associated organ dysfunction without TAMOF was not reviewed as part of the current updated guidelines. However, the wording of the prior 2020 statement that the panel could not suggest for or against the use of PLEX in children with sepsis or septic shock who meet criteria for TAMOF has now been clarified to more directly acknowledge that there was insufficient evidence to issue a recommendation for this sepsis subphenotype. Practically, however, the statement remains unchanged.

TAMOF is a severe inflammatory clinical subphenotype of sepsis (199). It is characterized by new-onset thrombocytopenia and progressive organ dysfunction, immune dysregulation, and coagulopathy. The pathogenesis of TAMOF is mediated through reduced activity of a disintegrin and metalloproteinase with thrombospondin type 1 motif (ADAMTS-13) enzyme, elevated von Willebrand factor (VWF) activity, and the presence of ultra-large plasma VWF that promote microangiopathy with microvascular thrombosis to drive MODS. TAMOF occurs in approximately 8% of children with sepsis and is associated with high mortality (200).

PLEX is a blood purification therapy that removes inflammatory mediators, ultra-large VWF multimers, and inhibitors of ADAMTS-13 (201, 202). In doing so, PLEX has the potential to improve patient outcomes by reducing and/or reversing the microvascular thromboses seen in TAMOF. However, definitive evidence supporting a benefit for PLEX for sepsis-associated TAMOF in children is not yet available.

For the 2020 guidelines, three studies were considered (203–205). One was a prospective multicenter observational study of 81 children with sepsis-associated TAMOF that found PLEX to be associated with greater improvement in organ dysfunction scores by day 4 (mean Pediatric Logistic Organ Dysfunction [PELOD]-2 decline, –7.9 points; 95% CI, –10.8 to –5.1) compared with no change in the non-PLEX group (203). Multivariable regression demonstrated lower 28-day mortality with PLEX (aRR, 0.45; 95% CI, 0.23–0.90), a finding that was consistent using a propensity score analysis (aRR, 0.46; 95% CI, 0.22–0.97). No PLEX-related serious adverse events were reported. However, ongoing risk of confounding due to imbalance in the size and clinical characteristics of the PLEX and non-PLEX groups, as well as inclusion of patients without sepsis, were noted by the panel. A second study was a retrospective analysis from the Turkish TAMOF Network that reported lower 28-day mortality with PLEX vs. no PLEX in 42 children (27% vs. 70%; $p = 0.004$) (204). The third study randomized 10 children to either PLEX or standard therapy. The five who received PLEX had restoration of ADAMTS-13 activity and greater survival compared with standard therapy (5/5 vs. 1/5; $p < 0.05$) (205).

The panel did not identify new studies since the 2020 guidelines, and thus, it remains reasonable to either treat children with sepsis or septic shock who meet criteria for the TAMOF subphenotype with or without PLEX. The inability to issue a recommendation aligns with the "category III indication" (uncertain benefit) for the use of PLEX in patients sepsis and MODS, as provided by the American Society for Apheresis (206). The panel noted that well-designed RCTs on this topic are urgently needed in children with TAMOF to determine if PLEX improves survival or organ recovery. Until then, use of PLEX should be individualized and based on local expertise and resources, noting that PLEX may not even be accessible in resource-limited settings.

52. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation on the use of extracorporeal blood purification.

Change From 2020 Guidelines: New recommendation.

Rationale: Extracorporeal blood purification therapies remove, adsorb, modulate, and/or replace circulating proteins, toxins, or cells with the goal of interrupting inflammatory cascades that potentiate organ dysfunction and restoring hemodynamic stability and organ function. Extracorporeal blood purification therapies such as hemofiltration and PLEX are discussed elsewhere in these guidelines; thus, here the panel focused on adsorptive modalities.

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In a report from an expert panel Delphi-based consensus statement on extracorporeal blood purification in critically ill children in European PICUs, there was general agreement that extracorporeal blood purification could be applied to septic shock, particularly with sepsis-associated MODS or TAMOF or when shock was refractory to usual care (207). This consensus was largely based on expert opinion from small observational studies, and panel noted the moderate-to-high cost of this therapy, a potential for risk, and the lack of availability in resource-limited settings. Thus, the panel could not issue a recommendation on use of adsorptive technologies for extracorporeal blood purification in children with sepsis or septic shock. RCTs are needed to determine the utility of extracorporeal blood purification using absorptive modalities in children with sepsis and septic shock.

53. For children with sepsis or septic shock, we suggest using venovenous ECMO when refractory hypoxia is present despite other therapies (conditional recommendation, very low certainty of evidence).

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

54. For children with septic shock, we suggest using veno-arterial ECMO as a rescue therapy only if shock is refractory to all other treatments (conditional recommendation, very low certainty of evidence).

Change From 2020 Guidelines: No change, carried over.

Rationale: See 2020 Guidelines for rationale.

M. IMMUNE THERAPIES

55. For children with sepsis or septic shock, there was insufficient evidence to issue a recommendation on whether to taper or discontinue immunosuppressive therapies.

Change From 2020 Guidelines: New recommendation.

Rationale: Children who are receiving immunosuppressive therapies for the management of comorbid conditions, such as malignancy, autoimmune disease, and organ transplantation, are at high risk for the development of sepsis. In this setting, the reconstitution of a robust host immune response to infection is likely to be important for sepsis recovery, and, thus, tapering or discontinuing immunosuppressive therapies has historically been a common feature of sepsis care in the immunocompromised host (208–211). In addition, the potential adverse effects of some immunosuppressive medications (e.g., calcineurin inhibitors), especially in the setting of reduced metabolism and/or clearance, may exacerbate sepsis-induced organ dysfunction. On the other hand, tapering or withholding of immunosuppressive therapies also carries a theoretical risk of underlying disease progression/relapse or graft rejection. Recent adult evidence suggests that, in some cases, continuation of immunosuppressive therapies in solid organ transplant recipients who develop sepsis may be associated with improved outcomes compared with reduction or discontinuation of these therapies (212, 213). However, there are no data on the impact of tapering/discontinuing or continuing immunosuppressive therapies during sepsis in children, including no data from RCTs. Therefore, the panel could not issue a recommendation on this issue. Until further data are available, decisions around the management of immune suppression need to be individualized based on a collaborative assessment of risks and benefits that considers host defence, disease progression/relapse, and pattern of organ dysfunction.

56. For children with sepsis or septic shock, we suggest against the routine use of IV immunoglobulin (IVIG; conditional recommendation, low certainty of evidence).

Remark: The routine use of IVIG is not recommended. However, select patients, such as those with primary humoral immunodeficiencies or immunocompromising comorbidities with documented low immunoglobulin levels, may benefit from such treatment.

Change From 2020 Guidelines: No change after review.

Rationale: The biologic rationale for IVIG in the management of infections, including sepsis and septic shock, is to boost passive immunity through neutralization of bacterial toxins, promote opsonization of bacteria, and inhibit immune cell proliferation and inflammatory mediators. However, IVIG has considerable batch-to-batch variability and its true biologic activity is not clear. Furthermore, despite these theoretical benefits, a clear benefit for IVIG as a routine immune therapy in pediatric sepsis has not been substantiated and the panel again issued a conditional recommendation against the routine use of IVIG.

Since the previous literature review for the 2020 guidelines, two new observational studies (214, 215)

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and one new RCT (216) were identified. In one study of 304 children with septic shock (median age 24 mo in the IVIG group and 48 mo in the non-IVIG group), hospital mortality was lower in the IVIG group (43% vs. 52%) but this difference was not statistically different and the IVIG group was observed to have longer durations of mechanical ventilation, PICU stay, and hospital stay and an increased proportion treated with CRRT (214). A second recent observational study reported that a higher percentage of patients with toxic shock syndrome treated with IVIG had residual morbidity at discharge than the non-IVIG control group (53% vs. 13%), although this endpoint was not well defined (215). A recent RCT on the use of IVIG in toxic shock syndrome included 28 pediatric patients and found that duration of mechanical ventilation, PICU and hospital LOS, and neurologic long-term outcomes were not different after randomized allocation to IVIG or 4% albumin (216).

A meta-analysis of nine studies combining 3973 infants with suspected or proven serious infection found that neither mortality nor major disability were significantly different between those treated with or without IVIG (217). Furthermore, a subanalysis of four studies with 266 infants found that treatment with immunoglobulin M (IgM)-enriched IVIG for suspected infection was also not associated with improved mortality (RR, 0.68; 95% CI, 0.39–1.20). Another recent meta-analysis of IgM- and immunoglobulin A (IgA)-enriched polyclonal IVIG in children with sepsis that included 13 neonatal and two pediatric studies found that mortality was lower in patients who received treatment with the IgM-enriched immunoglobulin compared with controls (OR, 0.41; 95% CI, 0.32–0.55) (218). However, data from adult patients with septic shock and necrotizing fasciitis do not support a routine benefit of IVIG (219, 220).

Based on the lack of consistent benefit, the panel continued to suggest against the routine use of IVIG in children with sepsis or septic shock. However, polyclonal IVIG could be considered for select patients, such as those with primary humoral immunodeficiencies or immunocompromising comorbidities with documented low immunoglobulin levels. Further high-quality RCTs are needed to clarify the utility of IgM- and IgA-enriched formulations in targeted subgroups.

57. For children with sepsis or septic shock with evidence of leukopenia or immunoparalysis, there was insufficient evidence to issue a recommendation on the use of an immune stimulant.

Change From 2020 Guidelines: New recommendation.
Rationale: Sepsis includes a spectrum of immune derangements with components of severe systemic inflammation, acquired immune suppression, or a combination of both (221). The immune suppressed phenotype, termed "immunoparalysis," has been characterized by reduced antigen presenting capacity as measured by low expression of human leukocyte antigen (HLA)-DR on the cell surface of monocytes, reduced ability of leukocytes to produce pro-inflammatory cytokines including tumor necrosis factor (TNF)-α upon ex vivo stimulation, and/or neutropenia and lymphopenia. While cytopenias can be identified in the clinical laboratory, other markers of immunoparalysis (e.g., monocyte HLA-DR expression, ex vivo TNF-α response) are currently limited to the research setting in most healthcare settings. In observational studies, such measures of immunoparalysis have demonstrated strong associations with adverse outcomes in critically ill children with infections, including increased mortality, prolonged organ dysfunction, and higher rates of healthcare-acquired infections (222–225). Multiple studies in critically ill adults and children have also shown that immunoparalysis can be reversed with immune stimulants, such as granulocyte macrophage-colony stimulating factor (GM-CSF) (222, 226, 227), interferon-γ (228–230) and anti-programmed death-ligand 1 antibodies (231). However, data from these relatively small RCTs have not confirmed that treatment with immune stimulation improves clinical outcomes, especially in children, in part due to insufficient statistical power.

Several large-scale prospective trials are currently in progress testing the impact of immune stimulants on clinical outcomes in critically ill children (232, 233). Until these data are available, the panel deemed current evidence insufficient to issue a recommendation on the routine use of immune stimulants in children with sepsis, even with evidence of leukopenia or immunoparalysis.

Notably, the panel supported guidelines issued by the American Society of Clinical Oncology Growth Factors Expert Panel that recommend use of granulocyte colony stimulating factor or GM-CSF in children

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with comorbid cancer diagnoses complicated by febrile neutropenia, including sepsis (234).

58. For children with sepsis or septic shock and hyperferritinemia, there was insufficient evidence to issue a recommendation on the use of immunosuppressive therapies.

Change From 2020 Guidelines: New recommendation.
Rationale: Hyperferritinemia (often defined as > 500 ng/mL) is a hallmark of many inflammatory syndromes that can be triggered by or complicate infections, particularly secondary hemophagocytic lymphohistiocytosis (sHLH), macrophage activation syndrome (MAS), and cytokine storm syndromes (e.g., multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2). These hyperinflammatory states share many overlapping clinical features with sepsis-associated MODS, including elevated blood ferritin levels, cytopenias, liver dysfunction, and coagulopathy. In some children with sepsis, extreme hyperferritinemia (blood ferritin > 10,000 ng/mL) has been associated with increased illness severity and mortality, raising the hypothesis that immune suppression may benefit those patients who exhibit a hyperinflammatory subphenotype, similar to the benefits of immune suppression in sHLH and MAS.

Despite this plausible biologic rationale, current evidence to support the use of immunosuppressive therapies (e.g., corticosteroids, anakinra, etoposide, cyclosporine) in children with sepsis and hyperferritinemia remained limited. Most available data derive from observational studies of pediatric patients with HLH/MAS, often in the context of rheumatologic disease or malignancy rather than sepsis alone. Available studies varied widely in their inclusion criteria, treatment protocols, and outcomes, which further limited generalizability. For example, retrospective studies have reported benefits of interleukin-1 blockade with anakinra in children with HLH/MAS, but these findings have not been reproduced in sepsis-specific populations (235–237). Similarly, a multicenter cohort of Turkish children with hyperferritinemia and MODS compared several combinations of immunosuppressive therapies, including corticosteroids and etoposide, without clear attribution to sepsis or comparison to usual care (238). Small case series have also explored HVHF or PLEX as immunomodulatory strategies in critically ill children with extreme hyperferritinemia, but none allocated treatments in a rigorous manner or offered adequate statistical power to assess for causal effects on clinical outcomes and, therefore, were not included in the evidence search for these guidelines (239–241).

While the concept of precision immunomodulation in pediatric sepsis is promising—particularly for patients with features of sHLH or cytokine storm, the safety of immunosuppression in children with active infection and heterogeneous immune competence remains uncertain. Future studies should prospectively define sepsis endotypes with hyperferritinemia, identify validated thresholds for risk stratification, and evaluate targeted immunosuppressive strategies using more rigorous methodology. Therefore, until further data about benefits and safety are available, the panel was unable to issue a recommendation on the use of immunosuppressive therapies for children with sepsis or septic shock and hyperferritinemia.

N. LONG-TERM FOLLOW-UP

59. For children with sepsis or septic shock, we suggest implementing an individualized, early rehabilitation bundle during the acute illness rather than not using a rehabilitation bundle (conditional recommendation, very low certainty evidence).

Change From 2020 Guidelines: New recommendation.
Rationale: Pediatric sepsis is associated with significant short- and long-term morbidity, affecting physical, psychosocial, emotional, and neurocognitive health (2, 20, 242). Early rehabilitation includes strategies to optimize comfort, reduce sedation, prevent delirium, promote sleep, facilitate early ventilator liberation, engage families, and encourage progressive mobility tailored to the child's age, condition, and premorbid functional level (15, 243).

There were no studies specifically focused on early rehabilitation for children with sepsis. However, key findings from general studies of critically ill children were deemed applicable. Early multimodal rehabilitation was associated with reduced duration of mechanical ventilation in one RCT (MD, –1 d; 95% CI, –1.53 to –0.47 d) and five observational studies (MD, –0.45 d; 95% CI, –0.89 to –0.010 d) (243–248), decreased risk of iatrogenic withdrawal in three observational studies (RR, 0.65; 95% CI, 0.49–0.87) (243, 245, 247), and lower incidence of delirium (RR, 0.85; 95% CI,

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0.69–1.03) in two pre-post and one observational studies (245, 248, 249). Physical function also shows a suggestion of improvement at hospital discharge with use of early rehabilitation strategies (MD, –1; 95% CI, –2.04 to 0.04) in three studies (207, 250–252), although a fourth study demonstrated worsening function (MD, 0.72; 95% CI, 0.34–1.1) (253). Notably, early mobilization of critically ill children appears safe with adverse events noted in only 5% of 1473 mobilizations across seven studies (247, 248, 250, 254–257) and no adverse events in 1030 mobilization events in five other studies (244, 245, 251, 258, 259). Safety in patients with sepsis remains uncertain, although a small adult RCT suggested harm is unlikely in septic shock (260).

The panel considered that most studies of early rehabilitation were from high-resource settings (244, 247, 250–254, 258, 261–264) and were unlikely to be generalizable to resource-limited settings. However, several studies have demonstrated that implementing rehabilitation protocols is feasible in settings with low PICU staffing (244, 252, 259) and non-technology–based interventions have been shown to be acceptable when equipment is limited (265, 266). In particular, participation of family members provided a cost-effective strategy to improve rehabilitation implementation and sustainability in resource-limited settings (252, 254, 255, 261–263). Still, there remains a need for additional research to assess safety, efficacy, and cost-effectiveness of early rehabilitation strategies in children with sepsis in both high- and low-resource settings.

60. For children with sepsis or septic shock, there was insufficient evidence to recommend for or against targeted post-hospital follow-up.

Change From 2020 Guidelines: New recommendation.
Rationale: Up to one-third of children who survive sepsis will suffer physical, cognitive, emotional and/or social sequelae after hospital discharge, that persist for months to years (267, 268). Children who survive sepsis hospitalization are also at risk for increased healthcare utilization, including an increased frequency of ED visits and hospital readmission (269–274). As such, post-hospitalization follow-up has been touted as having an important role in a child's overall recovery by helping to address new or worsening post-sepsis sequelae (274–276). Post-discharge follow-up has taken various forms including traditional outpatient clinic visits, phone calls, and written or recorded resources. Notably, there are many forms of follow-up (e.g., phone call) that may meet the needs of the child and his/her family without the need for substantial investment of time or resources from either the healthcare system or the child/family (e.g., travel to clinic, missed school/work).

There were no studies identified that specifically focused on children with sepsis or septic shock. However, evidence from four RCTs conducted in general PICU populations that included 8.7% of children (41/472) having sepsis was deemed applicable (277–280). Both the interventions (educational tool/program, behavioral interventional program and follow-up) and outcomes (neurocognitive functioning, child mental health, and parent mental health) varied across these studies, but overall demonstrated that a structured follow-up program was associated with fewer behavioral health problems and improved mental health (e.g., anxiety, depression, post-traumatic stress disorder) for both the child and family members. However, given the low proportion of patients with sepsis, the certainty of evidence was deemed insufficient to recommend for or against targeted post-hospital follow-up.

61. For children who survive sepsis or septic shock, it is reasonable to: 1) assess risk factors for post-sepsis morbidity; 2) educate the patient, family, and clinicians on the symptoms of post-sepsis morbidity; and 3) evaluate for new, long-term sequelae after hospital discharge (GPS).

Change From 2020 Guidelines: New recommendation.
Rationale: Children with higher severity of illness and organ dysfunction, longer duration of hospitalization, preexisting chronic comorbid conditions, older age (adolescents), and social vulnerabilities are at particularly high risk of neurobehavioral and cognitive morbidity after sepsis. In high-resource settings, several studies have identified that high Pediatric Risk of Mortality and PELOD scores, need for high-dose vasoactive medication doses, and prolonged hospitalization are associated with hospital readmission, mortality, and decline in health-related quality of life during the initial months following discharge (273, 281, 282). In low-resource settings, additional factors of malnutrition, maternal education, access to clean water, and living in rural areas have also been associated with mortality after hospital discharge (283–286).

Although the panel issued a GPS to screen children for risk factors associated with post-sepsis sequelae, provide education to patients, their families, and

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relevant clinicians about the symptoms of post-sepsis morbidity, and to evaluate for new long-term sequelae after hospital discharge, we are unable to provide recommendations on the optimal modality, timing, or type of follow-up. Further research is needed to determine the best mechanism by which to support children who survive sepsis and their families including the overall effectiveness of targeted follow-up after hospital discharge. Further consideration should be given to outcomes in alignment with the post-intensive care syndrome in pediatrics framework, including physical and social health (268). Evaluation of different follow-up approaches (e.g., clinic vs. phone vs. virtual visit) and timing must be considered. Finally, given the potential resources required for follow-up, the cost-effectiveness of targeted follow-up should be evaluated across geographical contexts, varied communities, and in low-, middle-, and high-resource settings.

KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES

In the 2020 iteration of these guidelines, 49 research priorities were identified across five topic areas (early recognition and infection, hemodynamics, ventilation, endocrine and metabolic therapies, and adjunctive therapies). New evidence published since the prior evidence search informed eight updated recommendations in these new guidelines, including statements about systemic screening for sepsis, performance improvement programs/treatment protocols, use of $Scvo_2$ and advanced hemodynamic monitoring, peripheral administration of vasoactive medications, and use of HVHF. In addition, the panel was able to issue a recommendation or GPS for 40% of the 20 new PICO questions. Unfortunately, 27 (90%) of the 29 recommendations that could be issued relied on low or very low certainty of evidence and no recommendation or GPS was able to be issued for 22 (36% of PICO questions). While these data highlight the need for ongoing and increased efforts to address existing knowledge gaps, we do note that several RCTs investigating crystalloid fluid type, timing of initiation of vasoactive medications, optimal blood pressure targets, and treatment with corticosteroids and other immunomodulating agents are currently in progress. In this guideline update, new or continued unmet research priorities are noted in the rationales provided with recommendations, but we also refer readers to the 2020 guidelines in which 29 pathophysiology questions warranting further study and 23 RCTs (i.e., total of 52 studies) were suggested as research opportunities (287).

Finally, the panel acknowledges that the recognition and treatment of children with sepsis or septic shock often begins in the pre-hospital setting, especially in low-resource settings where delays in access to healthcare systems may contribute to morbidity and mortality. While many of the recommendations in this guideline can be applied to the pre-hospital setting, focused studies to inform recommendations most applicable to the pre-hospital setting are needed.

ACKNOWLEDGMENTS

We acknowledge the important contributions to the guideline from Kristine Russell, our patient and family member. Also, we acknowledge the support of the following Society of Critical Care Medicine staff members in supporting the guideline development process, including Vishakha Kumar, MD, MBA, Hariyali Patel, MHA, and Dan Woznica, PhD.

Governance of the Surviving Sepsis Campaign Children Guidelines: Co-chairs: Niranjan Kissoon and Pierre Tissieres; Co-vice chairs: Scott L. Weiss and Mark J. Peters; Methods Co-Leads: Emilie Belley-Cote and Simon J. W. Oczkowski; Conflict-of-Interest Co-Chairs: Margaret M. Parker and Martin Kneyber; Subgroup Heads: David P. Inwald, Corinne Buysse, Akash Deep, Heidi R. Flori, and Luregn J. Schlapbach; Subgroup Methods Leads: Mark E. Nunnally, Karen L. M. Choong, Kusum Menon, and Srinivas Murthy; and Usability Co-Leads: Lauren Sorce and Cláudio F. Oliveira.

Sponsoring Organizations: Australian and New Zealand Critical Care Society; Canadian Critical Care Society; American Academy of Pediatrics; American Association of Critical-Care Nurses; American College of Chest Physicians; American Thoracic Society; Infectious Diseases Society of America; Pediatric Infectious Diseases Society; European Society for Pediatric and Neonatal Intensive Care; Society of Infectious Diseases Pharmacists; U.K. Sepsis Trust; and World Federation of Pediatric Intensive and Critical Care Societies.

Endorsing Organizations: Latin American Institute for Sepsis and the Latin American Society of Pediatric Intensive Care.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

These guidelines were solely funded by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine.

Dr. Randolph is an advisor for Inotrem and principal investigator (PI) on research study about influenza and respiratory syncytial virus/severe acute respiratory syndrome coronavirus 2 funded by the National Institute of Allergy and Infectious Diseases and Centers for Disease Control and Prevention. She was also an consultant for ThermoFisher (relationship ended). Dr. Deep is an advisor for Mallinckrodt and is the Medical President-Elect for the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Dr. Nishisaki is the PI on SMART PICU study funded by Agency for Healthcare Research and Quality (AHRQ) and is a researcher for Chiesi USA. Dr. Morrow is a board member of the World Federation of Pediatric Intensive and Critical Care Societies and the president of the Critical Care Society of Southern Africa. Dr. Buysse is a researcher for Zoll. Dr. De Luca is a speaker for Chiesi, Vyaire, and Medtronic. He is also a consultant for Getinge and Airway therapeutics. Dr. Carrol is chief investigator on the BATCH trial on procalcitonin funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme. She has received consulting fees for advisory panels paid directly to the University of Liverpool, from ThermoFisher, Biomerieux, and Danaher. Dr. Carlton is an independent contractor for UptoDate. Dr. Javouhey is a consultant for Sanofi. Dr. Balamuth is the co-principal investigator (Co-PI) on a trial evaluating normal vs. balanced fluids in pediatric sepsis funded by the National Institute of Child Health and Human Development (NICHD). Dr. Valla is a consultant for Baxter, Nutricia, and Nestle Health Science. Dr. Scott is the PI on randomized controlled trial (RCT) about screening funded by AHRQ. The trial ended in 2023. Dr. Flori is a scientific expert for Post & Schell PC (legal counsel firm). Dr. Lee is an investigator on the SHIPPS study funded by NIH. Dr. Zimmerman is the PI on the SHIPPS study funded by NIH and has received royalties by Elsevier Publishing. Dr. Wolf is a researcher for Karius and has received royalties by UptoDate. Dr. Fitzgerald was an independent contractor for BioPorto and is the PI/primary author on a study about sepsis-associated acute kidney injury funded by the NIH/National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Choong is co-investigator (CO-I) on SHIPPS trials funded by NIH and is a member of the Canadian critical care trials group. Lastly, she was the PI on research study about long-term outcomes post-PICU funded by AFP Innovation Fund. Dr. Remy is a member of Immune Functional Diagnostics, LLC. Dr. Menon is the PI on the SHIPPS trial funded by NIH and is the chair of the Canadian Critical Care Trials Group. Dr. Morin is a researcher on the use of blood purification devices for Baxter acute therapies. Dr. Schlapbach has or had received grants from MRFF, NIH, National Health and Medical Research Council (NHMRC), H2020, SNF, SPHN/PHRT, Thomas & Doris Ammann Foundation, and NOMIS foundation; he is currently involved in a trial on vitamin C and hydrocortisone in children with septic shock (investigator-led), the RESPOND trial; and he is chair of scientific affairs of ESPNIC. Dr. Peters is the PI on trials of conservative oxygenation strategies funded by U.K. NIHR HTA. Dr. Hall is the PI for a clinical trial and receives study drug (no charge) by Partner Therapeutics & Sobi. He is also the PI on a study about immune function & immune modulation funded by NIH. Lastly, he is an consultant for AbbVie and is a patent beneficiary for Kiadis. Dr. Carter is the Co-I on grant (not funded) related to IV immunoglobulin administration. Dr. Agus is Co-PI on SHIPPS trial funded by NIH and is a researcher for Dexcom. Dr. Tissieres is consultant and PI on a study about angiotensin-II funded by Paion; he is consultant and researcher for a grant on oXiris (continuous venovenous hemofiltration) funded by Baxter; and he provides consulting services on nirsevimab (monoclonal antibody) funded by Sanofi and is past president of ESPNIC. Dr. Raman is chief PI on a study about vitamin C and steroids funded by NHMRC and is a chief PI on study about beta-lactams (not started) funded by medical research futures (under embargo). Dr. Ray is Co-PI on PIVOTAL platform trial (not started) and is a Co-I on PRESSURE trial funded by NIHR. Dr. Faust received grants or contracts from Pfizer, Sanofi, GlaxoSmithKline, Johnson & Johnson, Merck, AstraZeneca, Valneva, Moderna, and BioNTech as clinical trial investigator on behalf of institution; honoraria for symposium participation paid to institution from Moderna, Pfizer, and Novavax; and honoraria for ad-boards participation paid to institution from AstraZeneca, MedImmune, Sanofi, Pfizer, Seqirus, Merck, Johnson & Johnson, and MSD. He is an investigator on the BATCH trial funded by NIHR. Dr. Weiss is the Co-PI on a trial evaluating normal vs. balanced fluids in pediatric sepsis funded by NICHD and has received honoraria from ThermoFisher Scientific for work related to procalcitonin in pediatric critical illness. Dr. Oczkowski is a consultant for VitalAire. Dr. Nadel is an advisor for Sanofi and GSK. Dr. Ranjit is the PI on a pilot RCT comparing epinephrine vs. norepinephrine as first-line vasoactive agent in pediatric septic shock. Dr. Manning is PI on OCEANIC study, Co-I on PRESSURE trial both funded by NIHR; he is Co-I on post-intensive care syndrome in pediatrics cohort study funded by NIH; and he is Nursing President-Elect of ESPNIC. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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These guidelines are intended for general information only, are not medical advice, and do not replace professional advice, which should be sought for any medical condition.

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